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(71) 出願人 (米国を除く全ての指定国について): 住友製薬株式会社 (SUMITOMO PHARMACEUTICALS COMPANY, LIMITED) [JP/JP]; 〒541-8510 大阪府 大阪市中央区 道修町2丁目2番8号 Osaka (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 堀内 良浩 (HORIUCHI,Yoshihiro) [JP/JP]; 〒561-0802 大阪府 豊中市 曽根東町 2-10-4-445 Osaka (JP).

(74) 代理人: 青山 葆, 外(AOYAMA,Tamotsu et al.); 〒540-0001 大阪府 大阪市中央区 城見1丁目3番7号IMPビル青山特許事務所 Osaka (JP).

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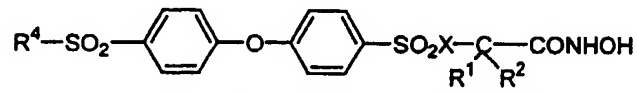
[続葉有]

(54) Title: HYDROXAMIC ACID DERIVATIVE AND MMP INHIBITOR CONTAINING THE SAME AS ACTIVE INGREDIENT

(54) 発明の名称: ヒドロキサム酸誘導体およびそれを有効成分とするMMP阻害剤

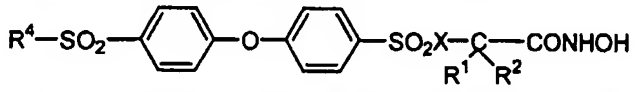


(1)

(57) Abstract: A hydroxamic acid derivative represented by the following general formula (1), which has selective MMP inhibitory activity: (1) wherein R^1 and R^2 each represents hydrogen, lower alkyl, lower haloalkyl, etc.; X represents methylene or NR^3 (R^3 represents hydrogen, lower alkyl, etc.); and R^4 represents C_{1-4} alkyl.

(57) 要約:

選択的MMP阻害活性を有する下記式



(1)

[式中、R^1およびR^2は水素原子、低級アルキル基、低級ハロアルキル基などを表わし、Xはメチレン基またはNR^3を表わし(ただし、R^3は水素原子、低級アルキル基などを表わす。)、そしてR^4は炭素数1～4の低級アルキル基を表わす。]

で表されるヒドロキサム酸誘導体。

GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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明　細　書

ヒドロキサム酸誘導体およびそれを有効成分とするMMP阻害剤

技術分野

本発明は、マトリックスメタロプロテイナーゼ(Matrix Metalloproteinases：以下MMPと略記する。)阻害作用を有するヒドロキサム酸誘導体、並びに該ヒドロキサム酸誘導体を有効成分として含有する医薬に関する。

背景技術

MMPは、例えば生殖、増殖および分化等の様々な生理学的過程において重要な役割を演じる蛋白質分解酵素である。正常な生理的条件下では多くのMMPの機能は生体組織内に存在するMMP阻害物質(Tissue inhibitor of metalloproteinase: TIMPs)により制御されている。

MMPは、活性中心に金属(例えば亜鉛)を有しており、MMPサブファミリーは現在、１８種類(MMP－１，MMP－２，MMP－３，MMP－７，MMP－８，MMP－９，MMP－１０，MMP－１１，MMP－１２，MMP－１３，MMP－１４，MMP－１５，MMP－１６，MMP－１７，MMP－１９，MMP－２０，MMP－２３，MMP－２４)が知られている。

近年、MMPの機能が異常に亢進すると、生体に存在するＴＩＭＰｓでは制御できなくなり、種々の疾患の原因となることが判ってきた。例えば、慢性関節リウマチや変形性関節症等の骨・軟骨系の疾患の場合、MMPの異常亢進により、関節軟骨の糖蛋白質やコラーゲンが減少する(J. Trzaskos, et al., Acta Onthopaedica Scandinavica, 66, 150 (1995))。また、MMPは動脈硬化の発現や血管形成術後の再狭窄にも重要な役割を示していると言われている(C. M. Dollery et al., Cric Res., 77, 863 (1995))。また、MMPは乳癌組織をはじめいくつかの癌組織において高度に発現していることが知られており、癌の増殖・転移において重要な役割を果たしている可能性が強く指摘されている(J. M. P. Freije et al., Journal of Biological Chemistry, Vol.269, 16766-16773,

1994)。また、ＭＭＰは、炎症を起こした歯茎から単離された繊維芽細胞中でも観察されている(J. Periodontal Res., 16, 417-424 (1981))。

更に、炎症性疾患の増悪因子であるＴＮＦαを潜伏型から発現型へ変換する酵素、ＴＮＦ変換酵素(TACE)(Nature, 370, 555-557 (1994))、アグリカナーゼ等もＭＭＰの範疇である。

中でも、ＭＭＰ－１３は、関節の軟骨の主要構成成分であるアグリカンを切断するアグリカナーゼとともに、関節に局在する酵素であり、軟骨のもう一つの主要構成成分であるII型コラーゲンに対して強い分解活性を有する酵素である。ＭＭＰ－１３は変形性関節症患者の軟骨に過剰発現されることが示されている(Mitchell, et al., J. Clin. Invest., 97, 761 (1996))。また、この過剰発現は骨関節炎やリューマチ性関節炎の患者の関節においても認められる。従って、ＭＭＰ－１３は軟骨や骨吸収に関わる因子とされ、これらを阻害する薬剤を用いた治療は原因療法となり得ると考えられている。

従って、ＭＭＰ－１３を阻害する化合物は、変形性関節症・リウマチをはじめとする関節炎や各種細胞の転移、浸潤もしくは増殖抑制剤などの疾患の治療剤および予防剤として有用であると考えられる。

一方で、変形性関節症および慢性関節リウマチの治療には、非ステロイド性抗炎症剤(ＮＳＡＩＤ)が広く用いられている。しかしながら、このような薬剤による治療方法は対症療法であり、疾患の進展を抑制する原因療法に用いられるような薬剤治療が求められている。

以上のように、ＭＭＰの機能亢進が種々の疾患の原因となっており、その活性を抑制するＭＭＰ阻害剤は、上記疾患の治療、および予防に有効であると考えられている。

具体的なＭＭＰ阻害剤としては、ヒドロキサム酸を有するアリールスルホンアミド誘導体等が報告されている。

例えば、ＷＯ ９７/２７１７４パンフレットには、α－アミノ酸のヒドロキサム酸誘導体が開示されている。また、ＷＯ ９９/５１５７２パンフレット、またはＵＳ Ｐａｔｅｎｔ ６１０７３３７には、フェノキシフェニル部分構造を有するα－アミノ酸のヒドロキサム酸誘導体が開示されている。

しかしながら、これまでに４－（４－アルキルスルホニルフェノキシ）フェニルスルホンアミドを部分構造に有する化合物は知られていない。

ＭＭＰ阻害剤については、種々の化合物について、癌、慢性関節リウマチ、変形性関節炎等について、臨床試験が行われた。しかし、これまでのＭＭＰ阻害剤の臨床試験報告では、これらの化合物の多くが被験者に骨格筋や関節に対する痛みなどの副作用を引き起こすことが報告されている。

この原因としては、ＭＭＰ－１やＭＭＰ－１４（ＭＴ１－ＭＭＰ）等のＭＭＰ阻害が注目されている（現代医療，32，931（2000）、蛋白質核酸酵素，45，1083（2000））。また、ＭＭＰノックアウトマウスではＭＭＰ－９、ＭＭＰ－１４ノックアウトマウスにともに骨形成異常が認められた。特にＭＭＰ－１４ノックアウトマウスでは、生後の発育で、コラーゲンの分解能の低下あるいは喪失による結合組織の代謝不全を原因とする表現型が現れたと考えられている（Kenn Holmbedk et al., Cell, 99, 81-92 (1999)）。つまり、骨・軟骨組織の組織リモデリングの際にコラーゲンの分解活性の低下や喪失が起こっていることが示唆されており、副作用への関与が大いに考えられる。

したがって、上記副作用を持たない、ＭＭＰ阻害剤の開発が求められていた。

発明の開示

本発明は、ＭＭＰ－３、および／または、ＭＭＰ－１３を選択的に阻害する化合物、並びにＭＭＰ－３、および／またはＭＭＰ－１３を選択的に阻害し、副作用の軽減されたＭＭＰ阻害剤を有効成分する医薬を提供することにある。

本発明者らは、ＭＭＰ－３および／またはＭＭＰ－１３と、ＭＭＰ－１４およびＭＭＰ－１との阻害選択性、更にＭＭＰ－２および／またはＭＭＰ－９との阻害選択性を検討することにより、主薬効と副作用との分離を大きくし、副作用を軽減できるのではないかと考えた。特に、骨格筋や関節に対する副作用の原因は、ＭＭＰ－１４を阻害することにあると考え、該ＭＭＰ－１４を阻害しない、ＭＭＰ－１３選択的阻害剤を得るべく、鋭意検討を行った。その結果、下記一般式（１）で示される４－（４－アルキルスルホニルフェノキシ）フェニル基を有する新規なヒドロキサム酸誘導体が優れたＭＭＰ－１３阻害活性を示す一方、ＭＭＰ－

９やMMP－１４の阻害活性が著しく低いことを見出した。

また、後記一般式(２)で示される化合物がMMP阻害剤として公知(WO ００/６３１９７パンフレット)であるが、MMP－１およびMMP－１４に対して非選択的であることを見出した。

本発明は以上の知見により完成するに至った。

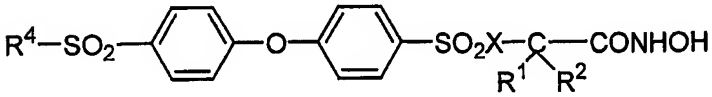
なお本明細書において、「MMP－１および／またはMMP－１４に対して非選択的」とは、該MMP－１および／またはMMP－１４に対して阻害活性が著しく低いか、あるいは阻害活性を示さないことを意味する。具体的には化合物のMMP－１、および／またはMMP－１４に対する阻害率(IC_{50}値)もしくはＫｉ値が、MMP－１３、および／またはMMP－３に対する５０％阻害率(IC_{50}値)もしくはＫｉ値に比べて極めて小さいことを意味する。

「MMP－１４に対して非選択的」とは、好ましくはMMP－１４に対するＩC_{50}値／MMP－１３に対するＩC_{50}値比が５０、より好ましくは１００、更に好ましくは３００以上である。

また、「MMP－１に対して非選択的」とは、好ましくはMMP－１に対するＩC_{50}値／MMP－１３に対するＩC_{50}値比が１００、より好ましくは５００、更に好ましくは１０００以上である。

発明を実施するための最良の形態

本発明は、一般式(１)



(1)

[式中、R^1およびR^2は、互いに独立して水素原子、置換もしくは無置換の低級アルキル基、または低級ハロアルキル基を表わすか、あるいはR^1およびR^2は互いに結合して、炭素数２～７の直鎖アルキレン基を表わすか、または式－(CH_2)m－Y－(CH_2)q－で表わされる基を表わし(ただし、Yは－O－、－NR^5－、－S－、－SO－、または－SO_2－を表わし、mおよびqは、互いに独立して１～５の整数を表わし、かつ、mとqとの和が２～６であり、そしてR^5は、水素原子、置換もしくは無置換の低級アルキル基、置換もしくは無置換の低級アル

キルカルボニル基、置換もしくは無置換の低級アルコキシカルボニル基、置換もしくは無置換の低級アルキルスルホニル基、置換もしくは無置換のスルファモイル基または置換もしくは無置換のカルバモイル基を表わす。)、Xは、メチレン基またはNR^3を表わし(ただし、R^3が水素原子、または置換もしくは無置換の低級アルキル基を表わすか、あるいはR^3はR^1と一緒になって、それらが結合するN原子と炭素原子と共に、置換もしくは無置換のヘテロシクロアルカンを形成してもよい。)、そしてR^4は、炭素数1～4の低級アルキル基を表わす。]で表されるヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグに関する。

本発明において、低級アルキル基とは、炭素数1～5の飽和の直鎖もしくは分枝のアルキル基を意味し、例えばメチル基、エチル基、プロピル基、1－メチルエチル基、ブチル基、1－メチルプロピル基、2－メチルプロピル基、1，1－ジメチルエチル基、ペンチル基、2，2－ジメチルプロピル基などが挙げられる。

低級アルコキシ基とは、前記の低級アルキル基に酸素原子が結合した基を意味し、例えばメトキシ基、エトキシ基、プロポキシ基、1－メチルエトキシ基、ブトキシ基、1－メチルプロポキシ基、2－メチルプロポキシ基、1，1－ジメチルエトキシ基、ペンチルオキシ基、2，2－ジメチルプロポキシ基などが挙げられる。

低級アルキルチオ基とは、前記の低級アルキル基に硫黄原子が結合した基を意味し、例えばメチルチオ基、エチルチオ基、プロピルチオ基、1－メチルエチルチオ基、ブチルチオ基、1－メチルプロピルチオ基、2－メチルプロピルチオ基、1，1－ジメチルエチルチオ基、ペンチルチオ基、2，2－ジメチルプロピルチオ基などが挙げられる。

低級アルキルスルフィニル基とは、前記の低級アルキル基にスルフィニルが結合した基を意味し、例えばメチルスルフィニル基、エチルスルフィニル基、プロピルスルフィニル基、1－メチルエチルスルフィニル基、ブチルスルフィニル基、1－メチルプロピルスルフィニル基、2－メチルプロピルスルフィニル基、1，1－ジメチルエチルスルフィニル基、ペンチルスルフィニル基、2，2－ジメチルプロピルスルフィニル基などが挙げられる。

低級アルキルスルホニル基とは、前記の低級アルキル基にスルホニルが結合した基を意味し、例えばメチルスルホニル基、エチルスルホニル基、プロピルスルホニル基、1-メチルエチルスルホニル基、ブチルスルホニル基、1－メチルプロピルスルホニル基、2－メチルプロピルスルホニル基、1，1－ジメチルエチルスルホニル基、ペンチルスルホニル基、2，2－ジメチルプロピルスルホニル基などが挙げられる。

低級アルキルカルボニル基とは、前記の低級アルキル基にカルボニルが結合した基を意味し、例えばアセチル基、プロパノイル基、ブタノイル基、2－メチルプロパノイル基、ペンタノイル基、2，2－ジメチルプロパノイル基などが挙げられる。

低級アルキルカルボニルオキシ基とは、前記の低級アルキルカルボニル基に酸素原子が結合した基を意味し、例えばアセチルオキシ基、プロパノイルオキシ基、ブタノイルオキシ基、2－メチルプロパノイルオキシ基、ペンタノイルオキシ基、2，2－ジメチルプロパノイルオキシ基などが挙げられる。

低級アルコキシカルボニル基とは、前記の低級アルコキシ基にカルボニルが結合した基を意味し、例えばメトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、1－メチルエトキシカルボニル基、ブトキシカルボニル基、1－メチルプロポキシカルボニル基、2－メチルプロポキシカルボニル基、1，1－ジメチルエトキシカルボニル基、ペンチルオキシカルボニル基、2，2－ジメチルプロポキシカルボニル基などが挙げられる。

ハロゲン原子とは、フッ素原子、塩素原子、臭素原子、またはヨウ素原子を意味し、好ましくはフッ素原子または塩素原子、特に好ましくは、フッ素原子である。

低級ハロアルキル基とは、1～5個のハロゲン原子で置換された前記低級アルキル基を意味し、例えばトリフルオロメチル基、ペンタフルオロエチル基、ジフルオロメチル基、2，2，2－トリフルオロエチル基、2，2－ジフルオロエチル基などが挙げられる。

低級ハロアルコキシ基としては、1～5個のハロゲン原子で置換された前記低級アルコキシ基を意味し、例えばトリフルオロメトキシ基、ペンタフルオロエト

キシ基、ジフルオロメトキシ基、2,2,2－トリフルオロエトキシ基、2,2－ジフルオロエトキシ基などが挙げられる。

炭素数2～7の直鎖アルキレン基としては、エチレン、n－プロピレン、テトラメチレン、ペンタメチレン、ヘキサメチレン、ヘプタメチレンなどが挙げられる。

低級シクロアルキル基としては、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基などが挙げられる。

低級シクロアルコキシ基としては、前記の低級シクロアルキル基に酸素原子が結合した基を意味し、例えばシクロプロポキシ基、シクロブトキシ基、シクロペンチルオキシ基、シクロヘキシルオキシ基などが挙げられる。

ヘテロシクロアルカンとしては、少なくとも1個の窒素原子を含み、その他に1個の窒素原子、1個の酸素原子、または1個の硫黄原子を含む4～7員のヘテロシクロアルカンが挙げられる。該ヘテロシクロアルカンが硫黄原子を含む場合、該硫黄原子は1または2個の酸素原子で酸化されていてもよい。

該ヘテロシクロアルカンとしては、アゼチジン、ピロリジン、ピペリジン、ピペラジン、モルホリン、チオモルホリン、チオモルホリンオキシド、チオモルホリンジオキシド、パーヒドロアゼピンなどが挙げられる。

アリール基としては、フェニル基、ナフチル基などが挙げられる。

アリールオキシ基とは、前記のアリール基に酸素原子が結合した基を意味し、フェノキシ基、1－ナフトキシ基、2-ナフトキシ基などが挙げられる。

アリールチオ基とは、前記のアリール基に硫黄原子が結合した基を意味する。

アリールスルホニル基とは、前記のアリール基にスルホニルが結合した基を意味する。

アリールカルボニル基とは、前記のアリール基にカルボニルが結合した基を意味する。

アリールカルバモイル基とは、前記のアリール基にカルバモイルが結合した基を意味する。

ヘテロアリール基とは、環内に0～3個の窒素原子、0もしくは1個の酸素原子、0もしくは1個の硫黄原子から選ばれる、1～3個のヘテロ原子を含む、単

環または2環のヘテロアリール基であり、例えばフリル基、チエニル基、ピロリル基、アゼピニル基、ピラゾリル基、イミダゾリル基、オキサゾリル基、イソオキサゾリル基、チアゾリル基、イソチアゾリル基、1，2，4－チアジアゾリル基、1，2，4－オキサジアゾリル基、トリアゾリル基、チアジアゾリル基、ピラニル基、ピリジル基、ピリダジニル基、ピリミジル基、ピラジニル基、インドリル基、ベンゾチエニル基、ベンゾフリル基、キノリル基、イソキノリル基、キナゾリル基、キノキサリニル基などが挙げられる。

ヘテロアリールオキシ基とは、前記のヘテロアリール基の、任意の炭素原子に酸素原子が結合した基を意味する。

ヘテロアリールチオ基とは、前記のヘテロアリール基の、任意の炭素原子に硫黄原子が結合した基を意味する。

ヘテロアリールスルホニル基とは、前記のヘテロアリール基の、任意の炭素原子にスルホニルが結合した基を意味する。

ヘテロアリールカルボニル基とは、前記のヘテロアリール基の、任意の炭素原子にカルボニルが結合した基を意味する。

ヘテロアリールカルバモイル基とは、前記のヘテロアリール基の、任意の炭素原子にカルバモイルが結合した基を意味する。

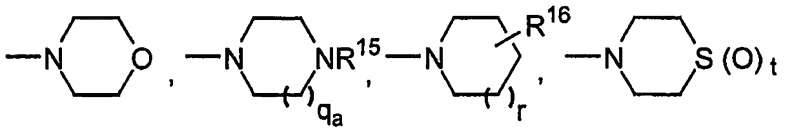
本発明における、アリール基、アリールオキシ基、アリールチオ基、アリールカルボニル基、アリールカルバモイル基、アリールスルホニル基、ヘテロアリール基、ヘテロアリールオキシ基、ヘテロアリールチオ基、ヘテロアリールカルボニル基、ヘテロアリールカルバモイル基、およびヘテロアリールスルホニル基が置換されている場合、同一または異なる、1～3個の置換基で置換されていてもよく、該置換基としては、以下のａ）～ｆ）が挙げられる。

ａ） ハロゲン原子、シアノ基、水酸基、カルボキシ基、低級ハロアルキル基、低級ハロアルコキシ基。

ｂ） 低級アルコキシ基、低級アルキルチオ基、低級アルキルスルフィニル基、低級アルキルスルホニル基、低級シクロアルキル基、低級アルコキシカルボニル基。

ｃ） $-CONR^{11}R^{12}$、$-SO_2NR^{11}R^{12}$。

[式中、R^{11}およびR^{12}は、互いに独立して、水素原子、低級アルキル基、低級アルコキシ基で置換されてもよい低級アルキル基を表わすか、$-NR^{11}R^{12}$は、下記の構造群から選ばれる１つの構造を意味する。



（式中、q_aは１または２の整数を表わし、ｒは０～２の整数を表し、ｔは０～２の整数を表わし、R^{15}は、低級アルキル基、低級アルキルカルボニル基、低級アルキルスルホニル基、または低級アルコキシカルボニル基を表わし、R^{16}は、カルボキシ基、水酸基、低級アルコキシ基、低級アルキルカルボニルオキシ基、低級アルキルカルボニル基、低級アルコキシカルボニル基、または１～２個の低級アルキル基で置換されていてもよいカルバモイル基を表わす。）]

ｄ） $-NR^{13}COR^{14}$、$-NR^{13}SO_2R^{14}$。

(式中、R^{13}およびR^{14}は、互いに独立して、水素原子、または低級アルキル基を表わす。)

ｅ） $-NR^{17}R^{18}$。

(式中、R^{17}は、水素原子または低級アルキル基を表わし、R^{18}は、水素原子、低級アルキル基、低級アルキルカルボニル基、低級アルコキシカルボニル基、または低級アルキルスルホニル基を表わす。)

ｆ） 無置換の低級アルキル基、または下記の１～３個の置換基で置換された低級アルキル基。

[該置換基とは、低級アルコキシ基、低級アルキルチオ基、低級アルキルスルフィニル基、低級アルキルスルホニル基、低級アルキルカルボニル基、低級アルコキシカルボニル基、低級アルキルカルボニルオキシ基、シアノ基、カルボキシ基、水酸基、$-NR^{17}R^{18}$(式中、R^{17}およびR^{18}は、前記と同義である。)、$-CONR^{11}R^{12}$、$-SO_2NR^{11}R^{12}$(式中、R^{11}およびR^{12}は、前記と同義である。)、$-NR^{13}COR^{14}$、または$-NR^{13}SO_2R^{14}$(式中、R^{13}およびR^{14}は、前記と同義である。)である。]

本明細書において、R^1およびR^2における、低級アルキル基が置換されている場合、同一または異なる置換基が１または複数個置換していてもよく、該置換基

としては、ハロゲン原子、水酸基、シアノ基、低級アルコキシ基、低級アルキルチオ基、低級アルキルスルフィニル基、低級アルキルスルホニル基、低級シクロアルキル基、置換もしくは無置換のアリール基、置換もしくは無置換のヘテロアリール基、置換もしくは無置換のアリールオキシ基、置換もしくは無置換のヘテロアリールオキシ基、置換もしくは無置換のアリールチオ基、置換もしくは無置換のヘテロアリールチオ基、置換もしくは無置換のアリールスルホニル基、置換もしくは無置換のヘテロアリールスルホニル基、$-NR^{17}R^{18}$(式中、R^{17}およびR^{18}は、前記と同義である。)などが挙げられる。

R^3における低級アルキル基が置換されている場合、同一または異なる、1～3個の置換基で置換されていてもよく、該置換基としては、以下のａ)～ｆ)が挙げられる。

ａ) カルボキシ基、水酸基、低級ハロアルキル基、低級ハロアルコキシ基、シアノ基。

ｂ) 低級アルキルカルボニル基、低級アルキルカルボニルオキシ基、低級アルコキシカルボニル基。

ｃ) $-CONR^{11}R^{12}$基、$-SO_2NR^{11}R^{12}$基、$-NHCONR^{11}R^{12}$基。

(式中、R^{11}およびR^{12}は、前記と同義である。)

ｄ) $-NR^{13}COR^{14}$、$-NR^{13}SO_2R^{14}$。

(式中、R^{13}およびR^{14}は、前記と同義である。)

ｅ) それぞれ、置換もしくは無置換の、アリール基、ヘテロアリール基、アリールオキシ基、ヘテロアリールオキシ基、アリールチオ基、アリールカルボニル基、ヘテロアリールカルボニル基、ヘテロアリールチオ基、アリールスルホニル基、ヘテロアリールスルホニル基。(前記ヘテロアリールとして、好ましくはフリル、およびチエニルが挙げられる。)

ｆ) それぞれ、同一または異なる１～３個の置換基で置換されていてもよい、低級アルコキシ基、低級アルキルチオ基、低級アルキルスルフィニル基、低級アルキルスルホニル基。

(上記 ｆ)における基が置換されている場合の置換基としては、置換もしくは無置換のアリール基、置換もしくは無置換のヘテロアリール基、低級アルコキシ基、

１もしくは２の低級アルキル基で置換されたカルバモイル基、および低級シクロアルキル基で置換されたカルバモイル基が挙げられる。ここで、ヘテロアリールとして、好ましくはフリル、およびチエニルが挙げられる。）

R^3がR^1と一緒になってそれらが結合するN原子および炭素原子と共に形成するヘテロシクロアルカンが置換されている場合、同一または異なる１～４個の置換基で置換されていてもよく、該置換基としては、以下のａ）またはｂ）が挙げられる。

ａ）置換基が炭素原子に結合している場合：

水酸基、カルボキシ基、低級アルキル基、低級アルコキシ基、低級アルコキシカルボニル基。

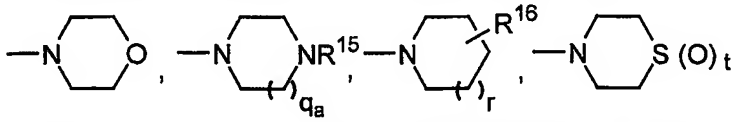
ｂ）置換基が窒素原子に結合している場合：

それぞれ置換もしくは無置換の低級アルキル基、低級アルコキシカルボニル基、低級アルキルカルボニル基、低級アルキルスルホニル基（この群の基における置換基としては、低級アルコキシ基、置換もしくは無置換のアリール基、置換もしくは無置換のヘテロアリール基が挙げられる。）；

それぞれ置換もしくは無置換のアリールカルボニル基、ヘテロアリールカルボニル基、アリールカルバモイル基（置換基としては、前記アリール基における置換基と同じものが挙げられる。）；

$-CONR^{11}R^{12}$、$-SO_2NR^{11}R^{12}$

[ここで、R^{11}およびR^{12}は、互いに独立して、水素原子、低級アルキル基、低級アルコキシ基で置換されてもよい低級アルキル基を表わすか、$-NR^{11}R^{12}$は、下記の構造群から選ばれる１個の構造を意味する。



（式中、q_a、ｒ、ｔ、R^{15}およびR^{16}は前記と同義である。）

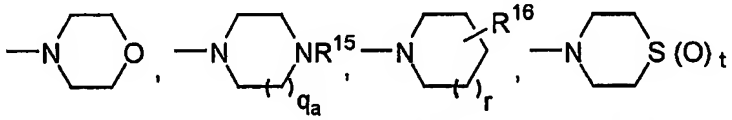
前記ヘテロアリール基およびヘテロアリールカルボニル基におけるヘテロアリールとして、好ましくはフリルまたはチエニルが挙げられる。

あるいは、該ヘテロシクロアルカンの隣り合う２個の炭素原子上の２個の置換基が結合して、それぞれ置換もしくは無置換のベンゼン環、または単環の芳香族

５～６員ヘテロ環を形成していてもよい。ここで単環の芳香族５～６員ヘテロ環としては、１～２個の窒素原子、１個の酸素原子、１個の硫黄原子から選ばれる１～２個のヘテロ原子を含む単環の芳香族５～６員ヘテロ環が挙げられる。具体的にはピリジン環、ピリミジン環、チオフェン環およびフラン環が挙げられる。前記ベンゼン環、および単環の芳香族ヘテロ環の置換基としては、前記アリール基における置換基と同じものが挙げられる。

R^5における低級アルキル基、低級アルキルカルボニル基、低級アルコキシカルボニル基、低級アルキルスルホニル基が置換されている場合、同一または異なる、1～３個の置換基で置換されていてもよく、該置換基としては、低級アルコキシ基、低級シクロアルコキシ基およびアリールオキシ基が挙げられる。

R^5におけるカルバモイル基およびスルファモイル基が置換されている場合、同一または異なる１～２の置換基で置換されていてもよく、該置換基としては、低級アルキル基および低級アルコキシ基が挙げられる。または、２個の置換基が隣接する窒素原子とともに結合して、下記の構造群：



（式中、q_a、r、t、R^{15}およびR^{16}は前記と同義である。）

から選ばれる１個の構造を形成していてもよい。

本発明において、一般式（１）におけるR^1およびR^2の好ましい態様の１つは、互いに同一の基を表わし、水素原子、または低級アルキル基である。更に好ましくは、水素原子、または炭素数１～３の低級アルキル基である。

R^1およびR^2が互いに結合して炭素数３～５のアルキレン基を表わすか、あるいはR^1およびR^2が結合して－(CH_2)m－Y－(CH_2)q－を表わし、mとqが共に２を表わすのもまた、好ましい態様である。また、前記において、Yが－S－または－O－であるものが好ましい。

Yが－NR^5－を表わす場合、R^5における、低級アルキル基、低級アルキルカルボニル基、低級アルキルスルホニル基、または低級アルコキシカルボニル基の置換基としては、前記R^3における低級アルキルの置換基と同じものが挙げられる。また、前記R^5における置換カルバモイル基の置換基としては、前記－CO

$NR^{11}R^{12}$におけるR^{11}およびR^{12}と同じものが挙げられる。

またR^1およびR^2のうちの一方が水素原子の場合、他方はエチル基、１－メチルエチル基、プロピル基、２－メチルプロピル基などの低級アルキル基である場合も好ましい態様の１つであり、このときのR^1およびR^2が結合する炭素原子の立体配置は、Ｄ体が好ましい(なお、本明細書において、Ｄ体とはＦｉｓｈｅｒ投影法に基づく表記に従う。)。

R^3は、好ましくは水素原子、炭素数１～４の低級アルキル基、またはカルボキシ基、フェニル基(該フェニル基は低級アルキル基、低級アルコキシ基またはハロゲン原子で置換されていてもよい。)、２－ピリジル基、３－ピリジル基、４－ピリジル基(該ピリジル基は低級アルキル基で置換されていてもよい。)、炭素数１～５の低級アルコキシカルボニル基および低級アルコキシ基からなる群から選ばれる基で置換された炭素数１～４の低級アルキル基であり、具体的には、水素原子、メチル、エチル、イソプチル、メトキシエチル、イソプロポキシエチル、エトキシエチル、メトキシプロピル、カルボキシメチル、カルボキシエチル、低級アルコキシカルボニルエチル、低級アルコキシカルボニルメチルなどである。

また、R^3がR^1と一緒になってそれらがそれぞれ結合するＮ原子と炭素原子と共に形成するヘテロシクロアルカンは、好ましくは、ピロリジン、ピペリジン、チオモルホリン、ピペラジンおよびモルホリンである。該ヘテロシクロアルカン上の炭素原子が置換されている場合の置換基として、好ましくはメチル、エチル、イソプロピル等の低級アルキル基が挙げられ、同一もしくは異なって、置換基が１～３個置換していてもよい。該ヘテロシクロアルカン上の窒素原子が置換されている場合の置換基として、好ましくは、それぞれフェニル等のアリール基、またはピリジル等のヘテロアリール基で置換されていてもよい低級アルキルカルボニル基、アルコキシカルボニル基、ヘテロアリールカルボニル基、アリールカルボニル基、－$CONR^{11}R^{12}$(R^{11}、R^{12}は、好ましくは水素原子、低級アルキルであるか、R^{11}とR^{12}がＮ原子と共に環を形成し、モルホリン、ピペリジン、ピロリジン、Ｎ－低級アルキルカルボニルピペラジン、Ｎ－低級アルキルピペラジン、ピペラジンを意味する。)が挙げられる。特に好ましくは、ベンジルオキシカルボニル基、メチル基、エチル基、イソプロピル基、ベンジル基、モルホリノカル

ボニル基、１－ピロリジニルカルボニル基、１－ピペリジニルカルボニル基、カルバモイル基、N,N－ジメチルカルバモイル基、２－ピリジルカルボニル基、３－ピリジルカルボニル基、４－ピリジルカルボニル基、アセチル基、プロピオニル基、２－フリルカルボニル基、２－チエニルカルボニル基、メタンスルホニル基、イソプロピルスルホニル基、ベンゾイル基、２－メトキシベンゾイル基、３－メトキシベンゾイル基、４－メトキシベンゾイル基、２－メトキシエチル基、２－エトキシエチル基などが挙げられる。

ここで、R^1が結合する炭素原子の立体配置は、D体が好ましい。

R^4は、好ましくは炭素数１～３の低級アルキル基であり、更に好ましくはメチル基である。

R^5は、好ましくは水素原子、炭素数１～４の低級アルキル基、または低級アルコキシ基もしくは低級シクロアルキル基で置換された炭素数１～４の低級アルキル基である。

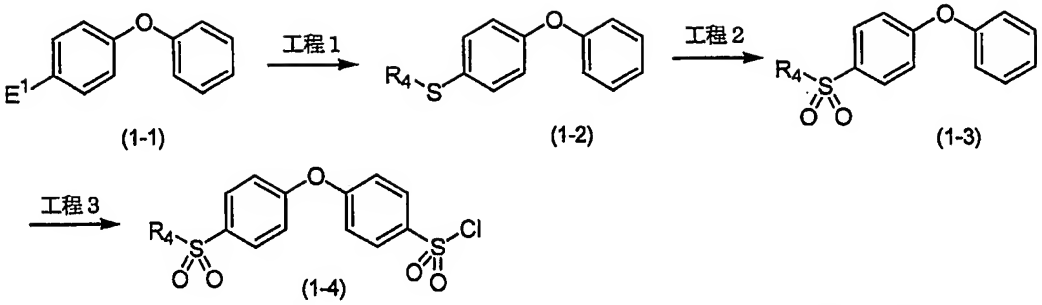
一般式(１)において、R^1およびR^2が、互いに独立して水素原子、または炭素数１～３の低級アルキル基であり、XがNR^3（該R^3がフェニル、ピリジル、炭素数１～５の低級アルコキシカルボニル、カルボキシ、または炭素数１～５の低級アルコキシで置換されていてもよい炭素数１～３の低級アルキル基である。）であり、そしてR^4がメチル基であるヒドロキサム酸誘導体が好ましい化合物である。

また一般式(１)において、R^1およびR^2が一緒になって、炭素数３～４の直鎖アルキレンを表わすか、式$-(CH_2)_2-O-(CH_2)_2-$を表わし、Xは$N-R^3$であり、該R^3が炭素数１～４の低級アルコキシ基で置換されていてもよい炭素数１～４の低級アルキル基であるヒドロキサム酸誘導体も好ましい化合物である。

以下に、本発明化合物(１)の製造方法を示す。

(製造法１：原料の製法)

４－(４－低級アルキルスルホニルフェノキシ)フェニルスルホニルクロリド



(式中、R^4は前記と同義であり、E^1はヨウ素原子または臭素原子を表わす。)

工程１：

式(１－１)の化合物に対して、有機金属試薬を反応させた後、ジスルフィドを作用させ、式(１－２)の化合物に導くことができる。ここで、有機金属試薬としては、例えば、ｎ－ブチルリチウム、sec－ブチルリチウム、tert-ブチルリチウム、メチルリチウム、フェニルリチウム等の有機リチウム試薬、イソプロピルマグネシウムブロミド、ジイソプロピルマグネシウム等の有機マグネシウム試薬などが挙げられる。ジスルフィドとしては、メチルジスルフィド、エチルジスルフィド、プロピルジスルフィド、イソプロピルジスルフィド、アリルジスルフィドなどが挙げられる。

溶媒としては、反応を阻害せず、出発物質をある程度溶解するものであれば特に限定されないが、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、ペンタン、ヘキサン、ヘプタン等の脂肪族炭化水素類、またはそれらの混合溶媒を挙げることができる。

反応温度は、－１００℃から室温で行われるが、好ましくは－７８℃から０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常３０分間から２４時間であり、好ましくは１時間から２４時間である。

工程２：

化合物(１－２)の化合物は、酸化剤で酸化することにより化合物(１－３)の化合物に導くことができる。ここで用いられる酸化剤としてはＯＸＯＮＥ(登録商標)、過酸化水素、メタクロロ過安息香酸、過酢酸などが挙げられる。

溶媒は、通常酸化反応に用いられる溶媒であれば特に限定されるものではない

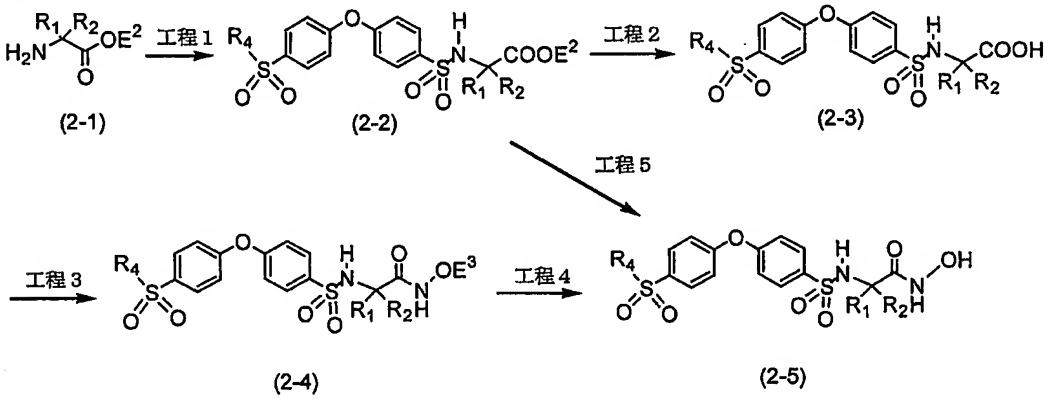
が、例えばジクロロメタン、ジクロロエタン等のハロゲン化炭化水素類、酢酸メチル、酢酸エチル等のエステル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、ペンタン、ヘキサン、ヘプタン等の脂肪族炭化水素類、メタノール、エタノール、イソプロパノール、ブタノール等のアルコール類、または水等が挙げられる。また、これらの混合溶媒を用いることもできる。反応温度は通常－１０℃から４０℃が好ましい。反応時間は３０分から２４時間が好ましい。

工程３：

式(１－３)の化合物は、クロロスルホニル化反応によって、式(１－４)の化合物へ導くことができる。クロロスルホニル化剤としては、クロロ硫酸を用いることができ、必要に応じて塩化チオニル共存下に反応を行うことができる。該クロロスルホニル化反応は、通常無溶媒で行われるが、反応を阻害せず、出発物質をある程度溶解するものであれば適当な溶媒を用いることもできる。

具体的な溶媒としては、ジクロロメタン、ジクロロエタン等のハロゲン化炭化水素類などを用いることができる。

(製造法２)



(式中、R^1、R^3、R^4は前記と同義であり、E^2はメチル、エチル、ベンジル、tertーブチルなどのカルボン酸の保護基を表わし、E^3は水素原子、トリメチルシリル基、ｔーブチルジメチルシリル基、ｔーブチル基、アリル基、ベンジル基等のヒドロキサム酸の保護基を表わす。)

工程１：

カルボニル基が保護された、式(２－１)の化合物と式(１－４)で表わされるアリールスルホニルクロライドから、塩基存在下または非存在下に、式(２－２)の

化合物に導くことができる。

使用される溶媒としては、反応を阻害せず、出発物質をある程度溶解するものであれば特に限定されないが、好ましくは、ジクロロメタン、クロロホルム、四塩化炭素、ジクロロエタン等のハロゲン化炭化水素類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、N,N－ジメチルホルムアミド、N,N－ジメチルアセトアミド、N-メチル－2-ピロリジノン、1,3-ジメチル－2-イミダゾリジノン、ジメチルスルホキシド等の非プロトン性極性溶媒、アセトニトリル等のニトリル類、酢酸メチル、酢酸エチル等のエステル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、ペンタン、ヘキサン、ヘプタン等の脂肪族炭化水素類、またはそれらの混合溶媒を挙げられる。

使用できる塩基としては、通常、アミド化の反応に使用されるものであれば、特に限定されないが、好ましくは、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、1,5－ジアザビシクロ[4.3.0]ノナー5－エン(DBN)、1,4－ジアザビシクロ[2.2.2]オクタン(DABCO)、1,8－ジアザビシクロ[5.4.0]ウンデカー7－エン(DBU)、ピリジン、ジメチルアミノピリジン、ピコリン、N－メチルモルホリン(NMM)等の含窒素有機塩基類、炭酸水素ナトリウム、炭酸水素カリウム、炭酸ナトリウム、炭酸カリウム等の無機塩基類などが挙げられる。

反応温度は、－２０℃から１５０℃の範囲で行われるが、好ましくは0℃から６０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常３０分間から４８時間であり、好ましくは３０分間から２４時間である。

工程２：

本工程は、式(２－２)の化合物のエステル基の脱保護により、式(２－３)の化合物へと導く工程である。本工程を実施するには、プロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(１９８１年)に記載されている方法が挙げられ

る。

具体的には、例えば以下のような方法で実施される。

(1)E^2がメチル基、エチル基等の低級アルキル基の場合、アルカリ加水分解、または酸加水分解によってカルボン酸へと導くことができる。すなわち、水酸化ナトリウム、水酸化カリウム、水酸化リチウム、水酸化マグネシウム等のアルカリ金属またはアルカリ土類金属の水酸化物の存在下、水とともに、反応に影響を与えないような溶媒、例えばメタノール、エタノール、イソプロパノール、ブタノール等のアルコール類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類の共存または非共存下において、通常、室温から加熱還流の温度範囲で、３０分間から２日間反応させることにより、式(２－３)の化合物を得ることができる。

酸加水分解においては、硫酸、塩酸等の鉱酸、トリフロロ酢酸、トリフロロメタンスルホン酸等の有機酸存在下に、水中で通常室温から加熱還流下に、３０分から２日間反応させることにより、式(２－３)の化合物を得ることができる。

(2)E^2がベンジル基の場合、パラジウム／カーボン、水酸化パラジウム、ニッケル等の遷移金属触媒の存在下、必要ならばギ酸アンモニウム等を添加して、水素ガス雰囲気下で撹拌することにより、式(２－３)の化合物へと導くことができる。

この際溶媒としては、メタノール、エタノール、イソプロパノール、ブタノール等のアルコール類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、酢酸エチル、酢酸メチル等のエステル類、またはそれらの混合溶媒を用いることができる。

(3)E^2がtert-ブチル基の場合、塩酸、ギ酸、パラトルエンスルホン酸、酢酸-臭化水素酸、トリフロロ酢酸等の酸、または、三フッ化ホウ素等のルイス酸を用いて式(２－３)に導くことができる。この際溶媒としてアセトニトリル、ジオキサンなどを用いることもできる。

工程３：

本工程は、式(２－３)の化合物のカルボキシル基を活性化した後、ヒドロキシルアミンまたは保護されたヒドロキシルアミンと反応させて行うことができる。ここで、保護されたヒドロキシルアミンとして適当なものはN,Oービス(トリメチルシリル)ヒドロキシルアミン、Oー(トリメチルシリル)ヒドロキシルアミンなどが挙げられる。

カルボキシ基の活性化方法としては、カルボキシ基を酸無水物法、混合酸無水物法、酸ハロゲン化物法、活性エステル法、または酸アジド法へ導く方法などが挙げられ、好ましくは酸ハロゲン化物法または混合酸無水物法である。

酸ハロゲン化物法を用いるときは、式(２－３)の化合物と、例えばオギザニルクロリド、塩化チオニル等のハロゲン化試薬を反応させて酸ハロゲン化物を調製した後、塩基の存在下でヒドロキシルアミンまたは保護されたヒドロキシルアミンと反応させ、式(２－４)を得ることができる。

ここで、塩基としては特に限定されないが、好ましくは、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、１,５ージアザビシクロ[４.３.０]ノナー５ーエン(ＤＢＮ)、１,４ージアザビシクロ[２.２.２]オクタン(ＤＡＢＣＯ)、１,８ージアザビシクロ[５.４.０]ウンデカー７ーエン(ＤＢＵ)、ピリジン、ジメチルアミノピリジン、ピコリン、Ｎーメチルモルホリン(NMM)等の含窒素有機塩基類、炭酸水素ナトリウム、炭酸水素カリウム、炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム等の無機塩基類などが挙げられる。

溶媒としてはジクロロメタン、クロロホルム、四塩化炭素、ジクロロエタン等のハロゲン化炭化水素類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、酢酸エチル、酢酸メチル等のエステル類、水、またはそれらの混合物が挙げられる。

反応温度は、－８０℃から１５０℃で行われ、好ましくは、通常－２０℃から８０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常１０分間から４８時間であり、好ましくは３０分間から２４時間である。

混合酸無水法を用いる場合は、式(２－３)の化合物を、塩基の存在下、酸ハロゲン化物と反応させることによって混合酸無水物とした後、ヒドロキシルアミンまたは保護されたヒドロキシルアミンと反応させ、式(２－４)の化合物に導くことができる。ここで、酸ハロゲン化物としてはメトキシカルボニルクロリド、エトキシカルボニルクロリド、イソプロピルオキシカルボニルクロリド、イソブチルオキシカルボニルクロリド、パラニトロフェノキシカルボニルクロリド、ｔ－ブチルカルボニルクロリドなどが挙げられる。塩基としては特に限定されないが、好ましくは、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、１，５－ジアザビシクロ[４．３．０]ノナ－５－エン(ＤＢＮ)、１，４－ジアザビシクロ[２．２．２]オクタン(ＤＡＢＣＯ)、１，８－ジアザビシクロ[５．４．０]ウンデカ－７－エン(ＤＢＵ)、ピリジン、ジメチルアミノピリジン、ピコリン、Ｎ－メチルモルホリン(NMM)等の含窒素有機塩基類、炭酸水素ナトリウム、炭酸水素カリウム、炭酸ナトリウム、炭酸カリウム等の無機塩基類などが挙げられる。

溶媒としては、ジクロロメタン、クロロホルム、四塩化炭素、ジクロロエタン等のハロゲン化炭化水素類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、酢酸エチル、酢酸メチル等のエステル類、またはそれらの混合溶媒が用いられる。

反応温度は、通常－４０℃から８０℃であるが、好ましくは、－２０℃から３０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常３０分間から４８時間であり、好ましくは３０分間から２４時間である。

また、式(２－３)の化合物と保護されたヒドロキシルアミンを、脱水縮合剤、および塩基存在下または非存在下に反応させ、式(２－４)の化合物に導くこともできる。

ここで縮合剤としては、ジフェニルホスホリルアジド(ＤＰＰＡ)、ジエチルホスホリルシアニド(ＤＥＰＣ)、ジシクロヘキシルカルボジイミド(ＤＣＣ)、カルボニルジイミダゾール(ＣＤＩ)、１－エチル－３－(３－ジメチルアミノプロピ

ル)カルボジイミド・塩酸塩(ＥＤＣ・ＨＣｌ)、Ｏ－(１Ｈ－ベンゾトリアゾール－1－イル)－１，１，３，３－テトラメチルーウロニウム　テトラヒドロボレイト(ＴＢＴＵ)、Ｏ－(１Ｈ－ベンゾトリアゾール－1－イル)－Ｎ，Ｎ，Ｎ’，Ｎ’－テトラメチルーウロニウム ヘキサフロロホスフェイト (ＨＢＴＵ)、(ベンゾトリアゾール－１－イルオキシ)トリス(ジメチルアミノ)ホスホニウムヘキサフルオロホスフェートなどを用いることができる。

溶媒は、特に限定されず、本工程の反応条件で反応しない溶媒であれば使用できる。具体的にはジクロロメタン、クロロホルム、四塩化炭素、ジクロロエタン等のハロゲン化炭化水素類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類、酢酸エチル、酢酸メチル等のエステル類、Ｎ，Ｎ－ジメチルホルムアミド、Ｎ，Ｎ－ジメチルアセトアミド、Ｎ－メチル－２－ピロリジノン、１，３－ジメチル－２－イミダゾリジノン、ジメチルスルホキシド等の非プロトン性極性溶媒、水、またはそれらの混合溶媒が用いられる。

塩基としては特に限定されないが、好ましくは、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、１，５－ジアザビシクロ[４．３．０]ノナー５－エン(ＤＢＮ)、１，４－ジアザビシクロ[２．２．２]オクタン(ＤＡＢＣＯ)、１，８－ジアザビシクロ[５．４．０]ウンデカー７－エン(ＤＢＵ)、ピリジン、ジメチルアミノピリジン、ピコリン、Ｎ－メチルモルホリン(ＮＭＭ)等の含窒素有機塩基類が挙げられる。

反応は、通常－１０℃から加熱還流下で行われるが、－２０℃から８０℃で行うことが好ましい。反応時間は、主に反応温度、使用される原料、および溶媒等の条件によって異なるが、通常３０分間から４８時間であり、好ましくは、３０分間から２４時間である。

その他、カルボン酸の活性化方法は、ＷＯ ００/６３１９７パンフレット、Comprehensive Organic Transformation (Larock, R. C., VCH Publishers, Inc. 1989)等に記載の方法に準じて実施される。

工程４：

化合物(２－４)においてE^{3}がヒドロキサム酸の保護基を表わす場合、本工程

により、脱保護することによって式(２－５)の化合物へ導くことができる。脱保護方法としては、それぞれの保護基に応じて、プロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(１９８１年)に記載されている方法などが用いることができる。具体的には、以下のような例を挙げることができる。すなわち、E^3がｔ－ブチルである場合は、トリフルオロ酢酸または塩酸など強酸による処理、E^3がベンジルである場合は、パラジウム/カーボンを用いた水素化分解、E^3がアリルである場合は、触媒としての塩化ビス(トリフェニルホスフィン)パラジウム(ＩＩ)の存在下で、水素化トリブチルスズおよび酢酸による処理などが挙げられる。また、E^3がトリメチルシリル基、もしくはｔ－ブチルジメチルシリル基である場合は、希塩酸等の酸性水溶液で処理することができる。

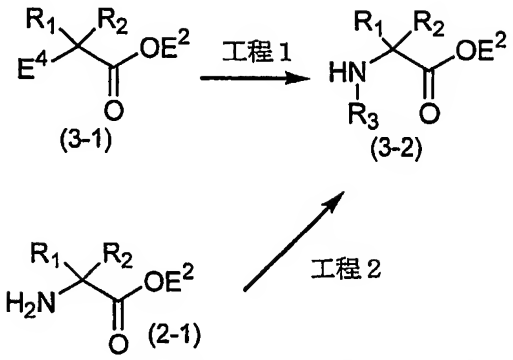
工程５：

式(２－２)の化合物は、ヒドロキシルアミンと反応させることによって、式(２－５)の化合物へ導くことができる。

例えば、ヒドロキシルアミン塩酸塩を、エタノール、プロパノール、メタノール等のアルコール系溶媒中、水酸化ナトリウム、水酸化カリウム、ナトリウムメトキシド、ナトリウムエトキシド、t-ブトキシカリウム等の塩基で処理することによって、遊離のヒドロキシルアミン溶液を調製し、式(２－２)の化合物と反応させる方法が挙げられる。

ここで、反応温度は、通常室温から１５０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常１０分間から４８時間であり、好ましくは、３０分間から２４時間である。該方法についてはＷＯ ００/６３１９７パンフレットに記載されている。

(製造法３：原料の製法)



(式中、R^1、R^2、R^3およびE^2は前記と同義であり、E^4は塩素原子、臭素原子またはヨウ素原子を表わす。)

工程１：

式(３－１)の化合物と、R^3-NH_2もしくはその塩とを、塩基存在下または非存在下に反応させ、式(３－２)の化合物に導くことができる。

ここで用いる塩基としては特に限定されないが、好適には、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、Ｎ－メチルモルホリン(NMM)等の含窒素有機塩基類が挙げられる。

溶媒としては、メタノール、エタノール、イソプロパノール、ブタノール等のアルコール類、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、および、N,N－ジメチルホルムアミド、N,N－ジメチルアセトアミド、N-メチル-２-ピロリジノン、１,３－ジメチル-２-イミダゾリジノン、ジメチルスルホキシド等の非プロトン性極性溶媒が好ましい。

反応温度は、－１０℃から加熱還流下で行われるが、好ましくは０℃から８０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常１時間から４８時間であり、好ましくは１時間から２４時間である。

工程２：

工程１と同様の方法で、式(２－１)の化合物と、R^3-Cl、R^3-Br、またはR^3-I等を用いて、式(３－２)の化合物を得ることができる。

あるいは、式(２－１)の化合物と、アルデヒドまたはケトンから調製したイミンに対して、ソディウムシアノボロヒドリドやソディウムトリアセトキシボロヒドリドなどのヒドリド還元剤を反応させて、式(３－２)の化合物に導くことがで

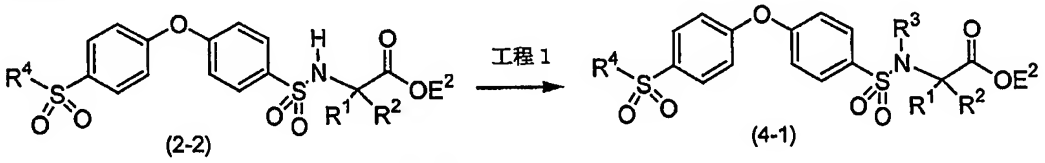
きる。

ここで、溶媒としては酢酸、プロパン酸等の有機酸、エタノール、メタノールなどのアルコール、ジクロロメタン、ジクロロエタン等のハロゲン化炭化水素類、アセトニトリル等を用いることができる。

反応温度は、－１０℃から加熱還流下で行われるが、好ましくは０℃から５０℃である。反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、通常１時間から４８時間であり、好ましくは１時間から２４時間である。

式(３－２)の化合物は、製造例２と同様の方法で、本発明の化合物へ導くことができる。

(製造法４)



(式中、R^1、R^2、R^3、R^4およびE^2は前記と同義である。)

工程１：

式(２－２)の化合物に対して塩基を作用させた後、R^3－Ｃｌ、R^3－Ｂｒ、R^3－Ｉ等のハロゲン化物と反応させることにより、式(４－１)に導くことができる。

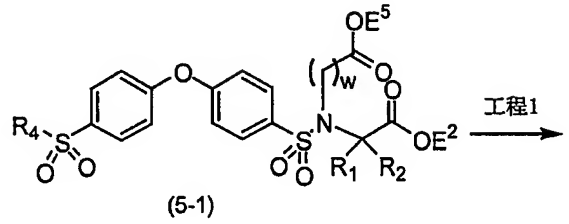
ここで、塩基としては炭酸カリウム、炭酸ナトリウム等の無機塩基、水素化ナトリウム、水素化リチウム等の水素化金属、カリウムヘキサメチルジシラジド、ナトリウムヘキサメチルジシラジド、ジイソプロピルアミドなどを用いることができる。

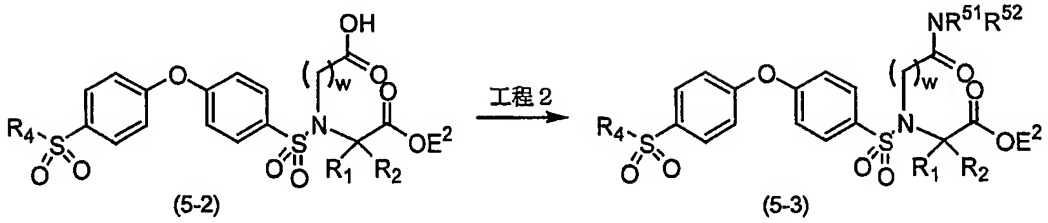
溶媒としては、ジエチルエーテル、ジイソプロピルエーテル、テトラヒドロフラン、ジオキサン等のエーテル類、および、Ｎ,Ｎ－ジメチルホルムアミド、Ｎ,Ｎ－ジメチルアセトアミド、Ｎ－メチル－２－ピロリジノン、１,３-ジメチル－２－イミダゾリジノン、ジメチルスルホキシド等の極性溶媒が好ましい。

反応時間は、主に反応温度、使用される原料および溶媒等の条件によって異なるが、好ましくは室温から加熱還流化下で、３０分間から７２時間撹拌することができる。

式(４－１)の化合物は、製造法２と同様の方法で、本発明の化合物へ導くことができる。

(製造法５)





(式中、R^1、R^2およびE^2は前記と同義であり、E^5は、E^2と異なる方法で脱保護可能なエステルの保護基を表し、R^{51}およびR^{52}はそれぞれ前記R^{11}およびR^{12}と同義であるか、R^{11}およびR^{12}に誘導可能な基を表わし、ｗは１～５の整数を意味する。)

工程１：

式(５－１)の化合物は、製造法３に記載された方法で製造することができる。式(５－１)の化合物は、製造法２に示した方法を用いて式(５－２)の化合物へ導くことができる。ただし、脱保護方法は、エステルE^2が脱保護されない条件を選択する。例えば、E^2がエチル基を表わし、E^5がベンジル基を表わす場合、接触還元を用いて選択的にE^5のみ脱保護することができる。該方法については、プロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(１９８１年)に記載されている。

工程２：

式(５－３)の化合物は、式(５－２)の化合物を塩基存在下、混合酸無水物とした後、アミン：$R^{51}R^{52}NH$と反応させ、式(５－３)の化合物へ導くことができる。混合酸無水物を用いた脱水縮合反応は、製造法２に示した方法で行うことができ

る。

あるいは、式(5－2)の化合物に対して適切な縮合剤存在下に、不活性溶媒中、塩基を用いて、アミン：$R^{51}R^{52}NH$を通常0℃から室温で1時間から48時間反応させることにより、式(5－3)の化合物に導くこともできる。

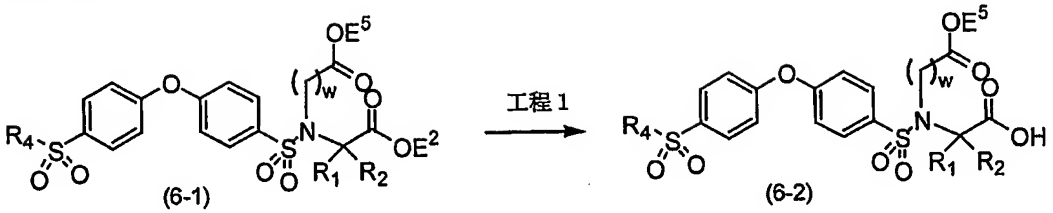
ここで縮合剤としては、実験化学講座(日本化学会編、丸善)22巻に表記されているものなどが挙げられる。例えば、シアノリン酸ジエチル、ジフェニルホスホリルアジド等のリン酸エステル類、1－エチル－3－(3－ジメチルアミノプロピル)-カルボジイミド･塩酸塩、ジシクロヘキシルカルボジイミド等のカルボジイミド類、2,2'－ジピリジルジスルフィド等のジスルフィド類とトリフェニルホスフィンのようなホスフィンの組合わせ、N,N'－ビス(2－オキソ－3－オキサゾリジニル)ホスフィニッククロリド等のリンハライド類、アゾジカルボン酸ジエチル等のアゾジカルボン酸ジエステルとトリフェニルホスフィン等のホスフィンの組み合わせ、2－クロロ－1－メチルピリジニウムヨーダイド等の2－ハロ－1－低級アルキルピリジニウムハライド類、1,1'－カルボニルジイミダゾールなどが挙げられる。

不活性溶媒とは、例えばテトラヒドロフラン、ジエチルエーテル、ジオキサン、1,2－ジメトキシエタン等のエーテル類、ヘキサン、ヘプタン、トルエン、ベンゼン、キシレン等の炭化水素類、ジクロロメタン、クロロホルム、1,2－ジクロロエタン等のハロゲン化炭化水素類、アセトン等のケトン類、アセトニトリル、N,N－ジメチルホルムアミド、N－メチル－2－ピロリジノン、1,3－ジメチル－2－イミダゾリジノン、ジメチルスルホキシド、ヘキサメチレンホスホアミド等の極性有機溶媒、またはこれらの混合溶媒等である。

塩基とは、通常の反応において塩基として使用されるものであれば特に限定されないが、例えばN－メチルモルホリン、トリエチルアミン、ジイソプロピルエチルアミン、トリブチルアミン、DBU、DBN、DABCO、ピリジン、ジメチルアミノピリジン、ピコリン等の含窒素有機塩基類、炭酸水素ナトリウム、炭酸水素カリウム、炭酸ナトリウム、炭酸カリウム等の無機塩基類などである。

式(5－3)の化合物は、製造法2に記載された方法を用いて、本発明の化合物(1)へ導くことができる。

(製造法６)



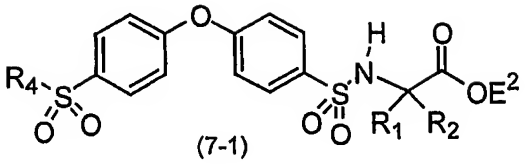
(6-1) (6-2)

(式中、R^1、R^2、R^4、w、E^2およびE^5は前記と同義である。)

工程１：

式(６－１)の化合物は、製造法３に記載された方法を用いて製造することができる。式(６－１)の化合物は、製造法２に示した方法を用いて式(６－２)の化合物へ導くことができる。ただし、脱保護方法は、エステルE^5が脱保護されない条件を選択する。例えば、E^5がエチル基を表し、E^2がベンジル基を表わす場合、接触還元を用いて選択的にE^2のみ脱保護することができる。該方法については、プロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(１９８１年)に記載されている。式(６－２)の化合物は、製造法２に記載された方法で、本発明の化合物(１)へと導くことができる。すなわち、－ＣＯＯE^2基をヒドロキサム酸へ変換することができる。更に、E^5を脱保護し、カルボキシ基へ変換することも可能である。

(製造法７)

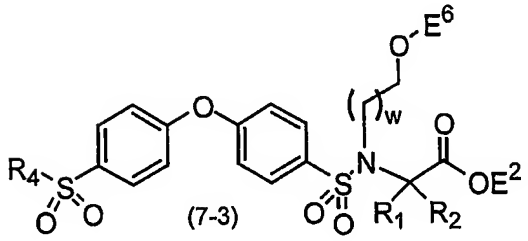


(7-1)

工程１

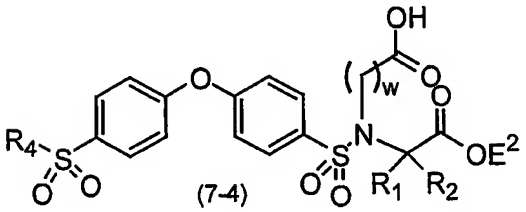
$E^6O\text{-}CH_2(CH_2)_n\text{-}E^1$

(7-2)



(7-3)

工程２



(7-4)

(式中、R^1、R^2、R^4、w、E^1およびE^2は前記と同義であり、E^6は、ｔ－ブチルジメチルシリル基等の水酸基の保護基、または置換されていてもよい低級アルキル基もしくは低級ハロアルキル基を表わす。)

工程１：

式(７－１)の化合物は、製造法２に記載された方法で、製造することができる。式(７－１)の化合物と式(７－２)の化合物を、製造法３に記載された方法で反応させることにより、式(７－３)の化合物を製造することができる。

工程２：

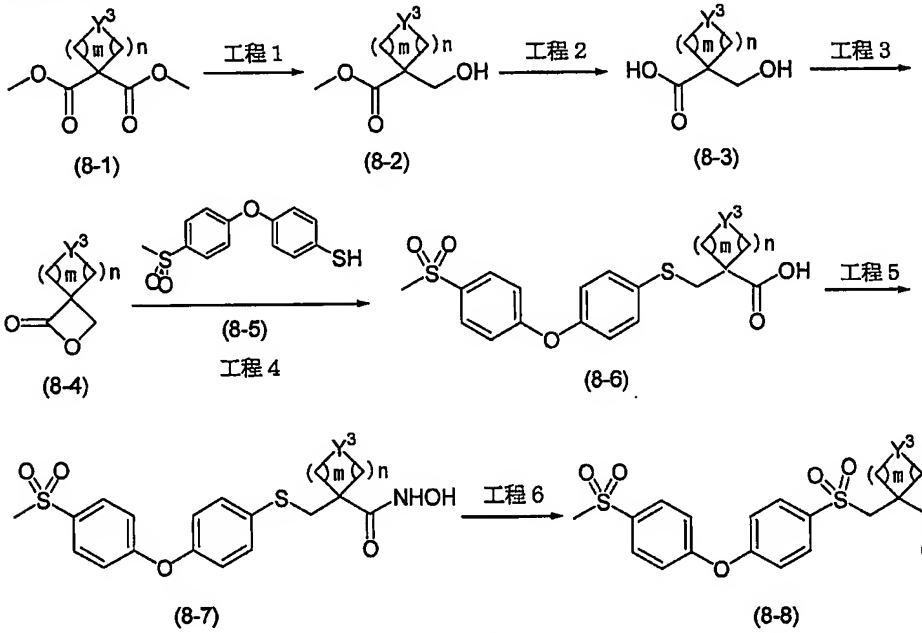
E^6が水酸基の保護基の場合、式(７－３)の化合物は、E^6を脱保護して、アルコール体とした後、水酸基を酸化することによって、式(７－４)の化合物へ導くことができる。

具体的には、例えばE^6がｔ－ブチルジメチルシリル基である時、三フッ化ホウ素エーテル錯体を塩化メチレン、クロロホルム等のハロゲン化炭化水素溶媒中で、０℃から室温で、約１５分から６時間反応させてE^6を脱保護し、中間体アルコールを形成させることができる。次いでアセトン溶媒中、ジョーンズ試薬を０℃か

ら室温で１５分から３０分間作用させることによって、式(７－４)の化合物に導くことができる。

式(７－４)の化合物のカルボキシル基を適当な保護基で保護した後、製造法５または６に記載された方法を用いて、本発明の化合物(１)を製造することができる。また、式(７－３)の化合物より製造法２と同様の方法を用いて、エステル部分をヒドロキサム酸へと変換し、本発明の化合物(１)へと導くことができる。

(製造法８)



(式中、mおよびnは前記と同義であり、Y^3は$-CH_2-O-$、$-NR^5-$または$-SO_2-$を表す。)

工程１：

還元剤により式(８－１)の化合物から式(８－２)の化合物に導く工程である。効果的な方法としては、一方のエステル基のみをアルデヒドに還元し、更にアルコールまで還元する方法である。－２０℃以下の温度(好適には-40℃から-20℃)にある(８－１)の不活性溶媒溶液(好適にはトルエンなど不活性芳香族溶媒)に適度に弱い還元剤(水素化ジイソプロピルアルミニウムなど)を作用させた後、メタノール、エタノールなどを添加する。更に、水素化ホウ素ナトリウムを加えて室温まで昇温させることで、(８－２)に導くことができる。

工程２：

エステルの加水分解工程である。メタノール等のアルコール類と水の共溶媒中の式(８－２)の化合物に、必要であればテトラヒドロフラン等のエーテル類を添加し,これに水酸化リチウムや水酸化ナトリウム等の塩基を加えて、５０℃から加熱還流下の温度で行うことができる。これを酸性条件で処理することで式(８－３)の化合物に導くことができる。

工程３：

式(８－３)の化合物に対して、適当な脱水剤を作用させてラクトン体：式(８－４)の化合物に導く工程である。

ジエチルエーテル等の不活性溶媒中の式(８－３)の化合物に対して、塩基としてトリエチルアミンなどの第３級アミン存在下に、トリフロロメタンスルホン酸無水物やメタンスルホン酸無水物などの脱水剤を作用させる方法が挙げられる。反応温度は氷冷下から室温が好ましく、反応時間は通常３０分間から１日間である。

工程４：

ラクトン：式(８－４)の化合物にチオール：式(８－５)の化合物のアニオンを作用させ､式(８－６)の化合物に導く工程である。

氷冷下から室温にあるジメチルホルムアミド等の非プロトン性極性溶媒やテトラヒドロフラン等のエーテル中の式(８－５)の化合物に対して水素化ナトリウムや水素化カリウムなどの塩基を作用させる。これに対して、式(８－４)の化合物を加えることにより式(８－６)の化合物に導くことができる。

ラクトンを作用させる温度としては０℃から６０℃が好ましく、反応時間は通常３０分から１２時間である。

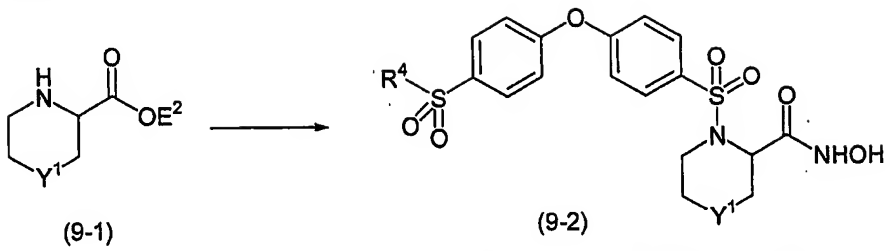
工程５：

カルボン酸：式(８－６)の化合物からヒドロキサム酸：式(８－７)の化合物に導く工程である。該工程は製造法２の工程３と同様にして行うことができる。好ましくは酸ハロゲン化法を用いる。

工程６：

スルフィド：式(８－７)の化合物から、スルホン：式(８－８)の化合物への酸化工程である。該工程は製造法１の工程２と同様にして行うことができる。

(製造法９)

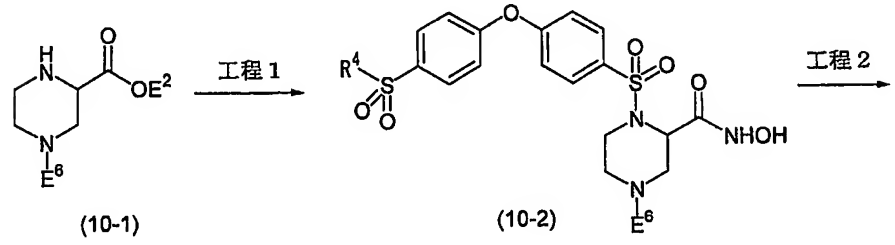


(9-1) (9-2)

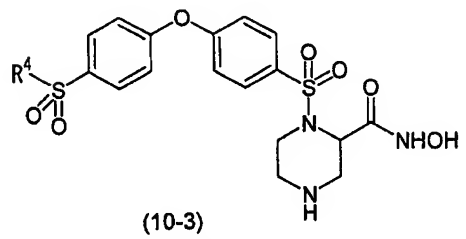
(式中、Y^1は単結合、メチレン、酸素原子または硫黄原子を表し、R^4およびE^2は前記と同義である。)

式(９－１)の化合物を原料に用いて、製造法２と同様にして、式(９－２)の化合物を合成することができる。ここで、式(９－１)の化合物は、公知の方法を用いて製造することができる。

(製造法１０)



(10-1) (10-2)



(10-3)

(式中、R^4およびE^2は前記と同義であり、E^6はE^2と異なる方法で脱保護可能なアミノ基の保護基を表わす。)

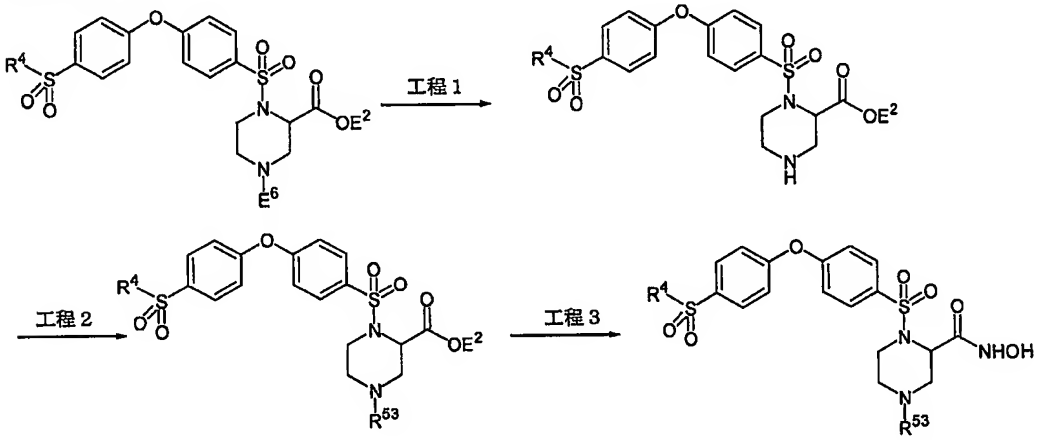
工程１：

式(１０－１)を原料に用い、製造法２と同様にして、式(１０－５)の化合物を合成することができる。E^6がアミノ基の保護基を表す場合、E^6とE^2の組み合わせとしては、例えば、ベンジル基とメチル基など低級アルキル基との組み合わせ、t-ブトキシカルボニル基とメチル基など低級アルキル基との組合わせなどである。式(１０－１)の化合物は市販品を用いるか、公知の方法で調製することができる。

工程２：

前記プロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(１９８１年)に記載された方法を用いて、式(１０－２)の化合物を脱保護することができる。

(製造法１１)



(式中、R^4、E^2およびE^6は前記と同義であり、R^{53}は式(１)においてR^3とR^1が一緒になって形成するヘテロシクロアルカンの置換基を表わす。)

工程１:

製造法１０と同様にして合成した式(１１－１)の化合物の保護基を脱保護することにより、式(１１－２)の化合物を合成することができる。ここで脱保護条件は、エステルの保護基E^2が反応しなければ特に限定されない。例えば、E^2がメチル基、エチル基などの低級アルキル基で、E^6がベンジルのとき、製造法２の工程２(２)に記載された方法を用いることができる。また、E^6がt－ブチルの場合、製造法２の工程２(３)に記載された方法を用いることができる。

工程２:

(R^{53}が低級アルキルカルボニル基、低級アリールカルボニル基、低級アルコキシカルボニル基、低級アルキルスルホニル基、低級アリールスルホニル基等で表される場合)

不活性溶媒中、トリエチルアミンなどの３級アミン、ピリジンなどの含窒素塩基または炭酸カリウム等の塩基存在下に、アシルクロリドなどアシルハライドを式(１１－２)の化合物に作用させる方法が挙げられる。ここで、不活性溶媒としてはジクロロメタンなどハロゲン化炭化水素類、テトラヒドロフラン等のエーテ

ル類が好ましい。反応温度は0℃から加熱還流下で行うことができ、0℃から室温が好ましい。また、カルボン酸を用いたときには、(製造法5)－工程2と同様にして合成することができる。

(R^{53}が低級アルキルカルバモイル基等で表される場合)

式(11－2)の化合物に対してイソシアネートを必要ならば、トリエチルアミンなどの3級アミン、ピリジンなどの含窒素塩基、不活性溶媒存在下に作用させる方法が挙げられる。または、式(11－2)の化合物に対して、不活性溶媒中、クロロギ酸4-ニトロフェニルやホスゲンなどを3級アミン存在下に反応させた後、1級または2級のアミンを作用させる方法が挙げられる。不活性溶媒としてはジクロロメタン等のハロゲン化炭化水素類、テトラヒドロフラン等のエーテル類、トルエン等の芳香族炭化水素類が好ましい。反応温度は0℃から加熱還流下であり、室温から加熱還流下が好ましい。

(R^{53}が置換もしくは無置換の低級アルキル基等で表される場合)

製造法3と同様の方法で合成することができる。

工程3:

製造法2と同様の方法で合成することができる。

上記において説明した製造法において、反応点以外の何れかの官能基が説明した反応条件下で変化するか、または説明した方法を実施するのに不適切な場合は、反応点以外を保護し、反応させた後、脱保護することにより目的化合物を得ることができる。保護基としては、例えばプロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis)、グリーン著、ジョン・ワイリー・アンド・サンズ・インコーポレイテッド(John Wiley & Sons Inc.)(1981年)等に記載されているような通常の保護基を用いることができ、更に具体的には、アミンの保護基としてはエトキシカルボニル、t-ブトキシカルボニル、アセチル、ベンジル等を、また水酸基の保護基としてはトリ低級アルキルシリル、アセチル、ベンジル等を挙げることができる。

保護基の導入および脱離は、有機合成化学で常用される方法[例えば、上記のプロテクティブ・グループス・イン・オーガニック・シンセシス(Protective Groups in Organic Synthesis) 参照]、あるいはそれらに準じた方法により行う

ことができる。

また、上記製造方法における、中間体、または最終生成物は、その官能基を適宜変換することによって、本発明に含まれる別の化合物へ導くこともできる。官能基の変換は、通常行われる一般的方法[例えば、コンプリヘンシブ・オーガニック・トランスフォーメーションズ(Comprehensive Organic Transformations)、R.C.ラロック(Larock)著(１９８９年)等参照]によって行うことができる。

上記各製造法における中間体および目的化合物は、有機合成化学で常用される精製法、例えば中和、濾過、抽出、洗浄、乾燥、濃縮、再結晶、各種クロマトグラフィー等に付して単離精製することができる。また、中間体においては、特に精製することなく次の反応に供することも可能である。

また、光学異性体は前記製造法の適切な工程で、光学活性カラムを用いた方法、分別結晶化法などの公知の分離工程を実施することで分離することができる。また、出発原料として式(１０－１)の化合物の光学活性体を使用することもできる。

本発明の化合物(１)が、光学異性体、立体異性体、互変異性体、および／または幾何異性体を有する場合、本発明の化合物(１)は、これらを含め、全ての可能な異性体およびそれらの混合物を包含する。

本発明の化合物(１)に、不斉炭素原子にもとづく１個以上の立体異性体が存在する場合、該異性体およびそれらの混合物もまた、本発明の範疇に含まれる。

本発明には、本発明の化合物(１)の薬学的に許容しうる塩もまた含まれる。本発明の化合物(１)が、カルボキシ基などの酸性基を有する場合、その塩基塩を製造するための物質として使用できる塩基は、それらの化合物と無毒性の塩基塩を形成するものである。それら無毒性塩基塩には、薬理学的に許容しうるカチオン、例えばアルカリ金属塩(例えばカリウム塩およびナトリウム塩)およびアルカリ土類金属塩(例えばカルシウム塩およびマグネシウム塩)、アンモニウムまたは水溶性アミン付加塩、例えばN－メチルグルカミン(メグルミン)、薬剤学的に許容しうる有機アミンの低級アルカノールアンモニウム塩その他の塩基塩が含まれるが、これらに限定されないし、これらの水等の薬剤学的に許容しうる溶媒和物でもよい。

本発明の化合物(１)が、ピリジルなどの塩基性基を有している場合、その酸付

加塩を製造するために用いる酸は、無毒性の酸付加塩、すなわち薬理学的に許容しうるアニオンを含有する塩類、例えば塩酸塩、臭化水素酸塩、ヨウ化水素酸塩、硝酸塩、硫酸塩、硫酸水素塩、リン酸塩、酸性リン酸塩、酢酸塩、乳酸塩、クエン酸塩、酸性クエン酸塩、酒石酸塩、酒石酸水素塩、コハク酸塩、マレイン酸塩、フマル酸塩、グルコン酸塩、サッカラート、安息香酸塩、メタンスルホン酸塩、エタンスルホン酸塩、ベンゼンスルホン酸塩、パラトルエンスルホン酸塩、パモエート[1,1′ーメチレンービスー(2ーヒドロキシー3ーナフトエート)]などの塩類を形成する酸である。

本発明の化合物(1)の塩を取得したいとき、本発明の化合物が塩の形で得られる場合には、そのまま精製すればよく、また、遊離の形で得られる場合には、適当な有機溶媒に溶解もしくは懸濁させ、酸または塩基を加えて通常の方法により塩を形成させればよい。

また、本発明の化合物(1)およびその薬理学的に許容される塩は、水あるいは各種溶媒との付加物の形で存在することもあるが、これら付加物も本発明に包含される。

本発明は、本発明の化合物(1)のプロドラッグも包含する。遊離のアミノ基、アミド基、ヒドロキシ基またはカルボキシル基をもつ化合物は、プロドラッグに変換できる。プロドラッグとしては、アミノ酸残基、または複数(例えば2～4個)のアミノ酸残基を含むペプチドが、ペプチド結合を介して遊離のアミノ基、ヒドロキシ基またはカルボキシル基に共有結合した化合物が挙げられる。

ここで、アミノ酸残基としては、同一もしくは異なる任意のアミノ酸残基が挙げられ、例えば20種類の天然アミノ酸、4ーヒドロキシプロリン、ヒドロキシリジン、デモシン、イソデモシン、3ーメチルヒスチジン、ノルバリン、βーアラニン、γーアミノ酪酸、シトルリン、ホモシステイン、ホモセリン、オルニチン、メチオニンスルホンなどが挙げられる。

また、プロドラッグとしては、ヒドロキサム酸基の酸素原子、および/または窒素原子に共有結合したカーボネート、カルバメート、アミドおよび低級アルキルエステルも含まれる。

また、本発明の化合物(1)がカルボキシル基を有する場合、例えばChemistry

and Industry, 1980, 435; Advanced Drug Discovery Reviews, 3, 39 (1989)に記載のプロドラッグなどが挙げられる。具体的には、カルボン酸の、エチルエステル等の低級アルキルエステル、エトキシカルボニルオキシメチル基等の低級アルコキシカルボニルオキシアルキルエステル、シクロヘキシルオキシカルボニルオキシ(1ーメチル)メチル基等の低級シクロアルコキシカルボニルオキシアルキルエステル、アシロキシメチルエステル、グリコレート、ラクテート、モルホリノエチルエステル等の生体内で分解されうるエステルが挙げられる。

また、本発明の化合物(1)が水酸基を有する場合のプロドラッグとしては、例えばアセチル基等のエステルが挙げられる。

本発明の化合物(1)、その薬学的に許容される塩、またはそれらのプロドラッグは、これを医薬として用いるにあたり、経口的または非経口的(例えば、静脈内、皮下、もしくは点滴剤、筋肉内注射、皮下注射、鼻腔内服剤、目薬、坐剤、経皮投与剤(軟膏、クリーム、ローション等)として投与することができる。経口投与のための形体としては、例えば、錠剤、カプセル剤、丸剤、顆粒剤、散剤、液剤、シロップ剤、懸濁剤などが挙げられ、非経口投与のための形体としては、例えば、注射用水性剤もしくは油性剤、軟膏剤、クリーム剤、ローション剤、エアロゾル剤、坐剤、貼付剤などが挙げられる。

これらの製剤は、従来公知の技術を用いて調製され、許容される通常の担体、賦形剤、結合剤、安定剤、滑沢剤、崩壊剤などを含有することができる。また、注射剤形で用いる場合には許容される緩衝剤、溶解補助剤、等張剤などを添加することもできる。また、適宜矯味矯臭剤を用いることもできる。

矯味矯臭剤としては、例えば、通常使用される、甘味料、酸味料、香料などを挙げることができる。

賦形剤としては、例えば、乳糖、白糖、ぶどう糖、マンニット、ソルビット等の糖誘導体；トウモロコシデンプン、バレイショデンプン、αーデンプン、デキストリン、カルボキシメチルデンプン等の澱粉誘導体；結晶セルロース、低置換度ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、カルボキシメチルセルロース、カルボキシメチルセルロースカルシウム、内部架橋カルボキシメチルセルロースナトリウム等のセルロース誘導体；アラビアゴム；デ

キストラン；プルランなどの有機系賦形剤；および軽質無水珪酸、合成珪酸アルミニウム、メタ珪酸アルミン酸マグネシウム等の珪酸塩誘導体；燐酸カルシウム等の燐酸塩；炭酸カルシウム等の炭酸塩；硫酸カルシウム等の硫酸塩；などの無機系賦形剤を挙げることができる。

滑沢剤としては、例えば、ステアリン酸、ステアリン酸カルシウム、ステアリン酸マグネシウム等のステアリン酸金属塩；タルク；コロイドシリカ；ビーガム、ゲイ蝋等のワックス類；硼酸：アジピン酸；硫酸ナトリウム等の硫酸塩；グリコール；フマル酸；安息香酸ナトリウム；ＤＬ－ロイシン；脂肪酸ナトリウム塩；ラウリル硫酸ナトリウム、ラウリル硫酸マグネシウム等のラウリル硫酸塩；無水珪酸、珪酸水和物等の珪酸類；および、上記澱粉誘導体などを挙げることができる。

結合剤としては、例えば、ポリビニルピロリドン、マクロゴール、前記賦形剤と同様の化合物を挙げることができる。

崩壊剤としては、例えば、前記賦形剤と同様の化合物およびクロスカルメロースナトリウム、カルボキシメチルスターチナトリウム、架橋ポリビニルピロリドンなどの化学修飾されたデンプン・セルロース類を挙げることができる。

安定剤としては、例えば、メチルパラベン、プロピルパラベン等のパラオキシ安息香酸エステル類；クロロブタノール、ベンジルアルコール、フェニルエチルアルコール等のアルコール類；塩化ベンザルコニウム；フェノール、クレゾール等のフェエノール類；チメロサール；デヒドロ酢酸；およびソルビン酸を挙げることができる。

経口投与用には、賦形剤を含有する錠剤を、種々の崩壊剤の他に、造粒結合剤と一緒に用いてよい。また、滑沢剤は、しばしば錠剤成形用に極めて有用である。同様の種類の固体組成物を、ゼラチンカプセル中の充填剤として用いてもよい（ここで好ましい材料には、ラクトースまたは乳糖、高分子量ポリエチレングリコールも含まれる）。経口投与用に水性懸濁剤および／またはエリキシル剤が望まれる場合、その活性成分は、種々の甘味剤、着香剤、着色剤または染料と一緒に、そして必要に応じて、乳化剤および／または懸濁化剤も、希釈剤と共に組合わせることができる。該希釈剤としては、水、エタノール、プロピレングリコー

ル、グリセリン、またはそれらの混合物が挙げられる。動物の場合、それらは、動物用飼料または飲料水中に５－５０００ppm、好ましくは２５－５０００ppmの濃度で含まれる。

非経口投与用(筋肉内、腹腔内、関節内、皮下および静脈内使用)には、通常、活性成分の滅菌注射用溶液を製造する。本発明の化合物のゴマ油もしくはラッカセイ油中かまたは水性プロピレングリコール中溶液を用いることができる。それら水溶液は、必要ならば、好ましくは８より大のｐＨで適当に調整され、緩衝液とすることができる。また液体希釈剤で等張にすることが好ましい。この水溶液は、静脈内注射用に適している。それら油状溶液は、関節内、筋肉内および皮下注射用に適している。無菌条件下でのこれら全ての溶液の製造は、当業者に周知の標準的な製剤技術によって容易に行われる。

鼻腔内投与または吸入による投与には、活性化合物は、患者が絞り出すもしくはポンプで放出するポンプスプレー容器からの溶液もしくは懸濁液の形で、または加圧式容器もしくはネブライザーからのエアゾルスプレー状態として、適当な噴射剤、例えば、ジクロロジフルオロメタン、トリクロロフルオロメタン、ジクロロテトラフルオロエタン、二酸化炭素または他の適当なガスを使用して、供給される。加圧式エアゾルの場合、投与単位は、計量された一定量を供給するバルブを与えることによって決定ができる。加圧式容器またはネブライザーは、活性化合物の溶液または懸濁液を入れることができる。吸入器または吹入器で用いるためのカプセルおよびカートリッジ(例えば、ゼラチンから製造される)は、本発明の化合物とラクトースまたはデンプンなどの適当な粉末基剤の粉末配合物を含有する製剤とすることができる。

また本発明の化合物は、カカオ脂または他のグリセリドなどの慣用的な坐剤基材を含有する坐剤または停留浣腸剤などの肛門用組成物中で製剤化できる。

本発明の化合物(１)、その薬学的に許容される塩、およびそれらのプロドラッグを投与する場合、その使用量は、症状、年齢、投与方法等によって異なるが、例えば、経口投与の場合には、成人に対して、１日当たり、下限として、０．０１ mg(好ましくは1 mg)、上限として、５０００ mg(好ましくは５００mg)を、１回または数回に分けて、症状に応じて投与することが望ましい。静脈内投与の場

合には、成人に対して、１日当たり、下限として、０．０１mg(好ましくは0.1mg)、上限として、１０００mg(好ましくは３０mg)を、１回または数回に分けて、症状に応じて投与することにより効果が期待される。

本発明の化合物(1)、そのプロドラッグ、およびそれらの薬学的に許容される塩はマトリックス金属プロテアーゼ阻害剤として有用である。したがって、過剰のまたは望ましくないマトリックス金属プロテアーゼに関係する疾患を治療または予防するのに使用される。

過剰のまたは望ましくないマトリックス金属プロテアーゼに関係する疾患としては、関節炎(例えば、変形性関節症およびリウマチ様関節炎)、炎症性腸疾患、クローン病、気腫、急性呼吸困難症候群、ぜん息、慢性閉塞性疾患、慢性気管支炎、気管支炎、アルツハイマー病、器官移植片毒性、悪液質、アレルギー反応、アレルギー性接触過敏症、アレルギー性結膜炎、アレルギー性鼻炎、癌(例えば固形腫瘍癌、例えば結腸癌、乳癌、肺癌および前立腺癌、および造血悪性、たとえば白血病およびリンパ腫)、組織潰瘍、再狭窄、歯周病、表皮水疱症、骨粗鬆症、人工関節移植片の弛緩、アテローム硬化症(例えば、アテローム硬化性局面破裂、アテローム性斑裂開)、大動脈瘤(例えば、腹部大動脈瘤および脳大動脈瘤)、うっ血性心不全、心筋梗塞、発作、大脳虚血、頭外傷、脊髄損傷、神経変性疾患(急性および慢性)、自己免疫疾患、ハンチントン病、パーキンソン病、片頭痛、うつ病、末梢神経障害、痛み、大脳アミロイド血管障害、ヌートロピックまたは認識増強、筋萎縮性側索硬化症、多発性硬化症、接眼レンズ脈管形成、角膜損傷、黄斑変性、異常創傷治癒、熱傷、糖尿病、糖尿病性末梢神経障害、糖尿病性網膜症、糖尿病性潰瘍、腫瘍浸潤、腫瘍増殖、腫瘍転移、角膜瘢痕、強膜炎、ＡＩＤＳ、敗血症、敗血性ショック、ざ瘡、急性感染、アルコール中毒、ＡＬＳ、過敏症、狭心症、血管線維腫、食欲不振、ＡＲＤＳ、アスピリン非依存性抗血栓症、アトピー性皮膚炎、良性増殖症、出血、骨折、火傷、悪液質、心筋症、大脳出血、大脳血管性痴呆、ＣＨＦ、慢性皮膚創傷、冠動脈血栓症、のう胞性線維症、褥瘡性潰瘍、デュシェーヌ筋ジストロフィー、気腫、子宮内膜症、表皮水疱症、眼病、線維症、胃炎、糸球体病、糸球体腎炎、痛風、移植拒絶反応、歯茎炎、ＧＶＨＤ、橋本甲状腺炎、頭部外傷、頭痛、血管腫、肝炎、多毛症、高血圧、イン

シュリン抵抗性、間隙性腎炎、虚血、虚血性心臓病、カポージ肉腫、角質化、角膜炎、腎不全、リーシュマニア症、らい病、白血病、白血球浸潤、肝硬変、マラリア、下顎関節病、記憶障害、髄膜炎、片頭痛、流産、多発脳梗塞性痴呆、筋ジストロフィー、筋肉痛、重症筋無力症、ミエニン分解症、心筋梗塞、近視、血管新生緑内障、神経炎、眼腫瘍、視神経炎、パジェット病、疼痛、膵炎、パーキンソン病、歯周炎、末梢血管病、結節性多発動脈炎、多発性軟骨炎、早産、胚膜早期裂開、プリオン病、増殖性網膜症、蛋白尿、偽痛風、乾癬、翼状片、肺気腫、放射線障害、ガラガラヘビ咬傷、ライター症候群、腎線維症、遠心咬合、再発性灌流障害、再狭窄、強膜炎、硬皮症、老年痴呆、老化、敗血症、敗血症性ショック、シャープ症候群、シェーグレン症候群、ＳＬＥ、脊椎分離症、狭窄症、不妊症、発作、鬱血性血栓症、化学療法による中毒症、中毒性ショック、結核、尿毒症、脈管炎、心室拡張、表皮水疱症およびメタロプロティナーゼ発現により特徴づけられる他の疾病。

特定の疾病の治療に本発明の化合物を用いる場合、本発明の化合物はその疾病のために使用される種々の存在する治療剤と組合わすことができる。リウマチ様関節炎または変形性関節症に対しては、本発明の化合物は、ＴＮＦα阻害剤、抗ＴＮＦモノクローナル抗体およびＴＮＦ受容体免疫グロブリン分子(Enbrel登録商標)、低用量メトトレキセート、レフニミド、ヒドロキシクロロキン、d-ペニシラミン、アウラノフィン、標準的非ステロイド抗炎症剤、例えばピロキシカム、ジクロフェナク、プロピオン酸類、例えばナプロキセン、フルルビプロフェン、フェノプロフェン、ケトプロフェンおよびイブプロフェン、フェナメート、例えばメフェナム酸、インドメタシン、スリンダク、アパゾン、ピラゾロン類、例えばフェニルブタゾン、サリチル酸類、例えばアスピリン、シクロオキシゲナーゼ(ＣＯＸ)２阻害剤、例えばメロキシカム・セレコキシブおよびロフェコキシブ、鎮痛剤および関節内治療剤、例えばコルチコステロイド、およびヒアルロン酸、例えばヒアルガンおよびシンビクス等と組合わせて使用することができる。

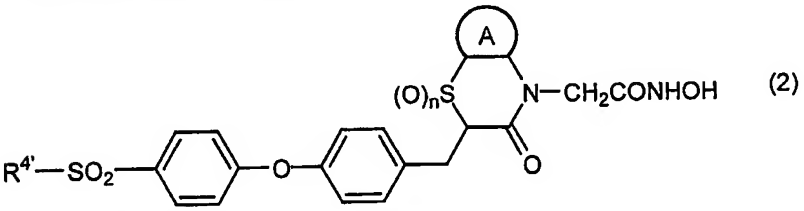
本発明の化合物はまた、抗癌剤、例えばエンドスタチンおよびアンジオスタチンまたは細胞毒性薬物、例えばアドリアマイシン、ダウノマイシン、シスプラチン、エトポシド、タキソール、タキソテレおよびアルカロイド、例えばビンクリ

スチン、および抗代謝物、例えばメトトレキサートと組合しても使用され得る。本発明の化合物はまた、心臓血管剤、例えばカルシウムチャネル遮断薬、脂質低下剤、例えばスタチン、フィブレート、β－遮断薬、ＡＣＥ阻害剤、アンジオテンシン－２受容体アンタゴニストおよび血小板凝集インヒビターと組合わせても使用できる。

本発明の化合物はまた、中枢神経系薬剤、例えば抗うつ剤(例えばセルトラリン)、抗パーキンソン薬剤(例えばデプレニル、Ｌ－ドーパ、レクィップ、ミラテックス、ＭＡＯＢインヒビター、例えばセレジンおよびラサギリン、comP阻害剤、例えばＡ－２阻害剤、ドパミン再摂取阻害剤、ＮＭＤＡアンタゴニスト、ニコチンアゴニスト、ドパミンアゴニスト、および神経酸化窒素合成阻害剤)、および抗アルツハイマー薬剤、例えばアリセプト、タクリン、ＣＯＸ２阻害剤、プロペントフィリン(propentofylline)またはメトロフォネートと組合わせて使用できる。

本発明の化合物はまた、骨粗鬆症剤、例えばドロロキシフェン、フォゾマックス、エチドロネートおよび免疫抑制剤、例えばＦＫ－５０６およびラパマイシンと組合わせも使用し得る。

本発明はまた、一般式(２)



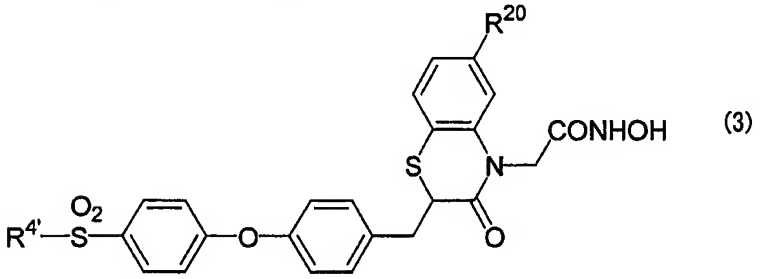
[式中、環Ａは置換または無置換のベンゼン環または芳香族５～６員ヘテロ環を表わし、$R^{4'}$は炭素数１～４の低級アルキル基を表わし、そしてｎは０～２の整数を意味する。]

で表わされる化合物を有効成分とするＭＭＰ－１およびＭＭＰ－１４に対して非選択的であることを特徴とするＭＭＰ－３および／またはＭＭＰ－１３阻害剤に関する。

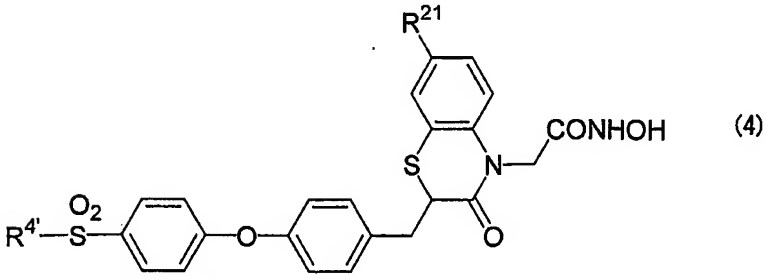
式(２)において、ｎは好ましくは０であり、$R^{4'}$は好ましくは炭素数１～３の低級アルキル基であり、更に好ましくはメチル基である。

式(2)中、環Aが置換されている場合、1～3の置換基で置換されていてもよい。環Aの置換基としては、前記アリール基またはヘテロアリール基における置換基と同じものが挙げられる。好ましくは環Aの置換基としては、カルボキシ基、シアノ基、ハロゲン原子、水酸基、低級アルキル基、置換もしくは無置換の低級アルキル基、低級アルコキシカルボニル基、低級アルコキシ基、低級アルキルスルホニル基、低級アルキル基で置換されていてもよいカルバモイル基、低級アルキル基で置換されていてもよいスルファモイル基が挙げられる。特に好ましくは、カルボキシ基、置換もしくは無置換の低級アルキル基が挙げられ、該低級アルキル基の置換基としては、水酸基、低級アルコキシ基、カルボキシ基、低級アルキル基で置換されていてもよいカルバモイル基、低級アルコキシカルボニル基などが挙げられる。

式(2)中、環Aは好ましくは、ベンゼン、ピリジン、チオフェン、ピラゾールである。式(2)で表される化合物の好ましい態様として、以下の式(3)または式(4)で表される化合物が挙げられる。



(3)



(4)

($R^{4'}$は前記と同義であり、R^{20}およびR^{21}は環Aにおける置換基と同義である。)

式(2)で示される化合物は、上記の化合物(1)の場合と同様にして投与される。

なお、式(2)で示される化合物は公知であり、WO 00/63197パンフレットに記載の方法により製造することができる。

実施例

以下実施例を挙げて本発明を詳細に説明するが、本発明はこれらに限定されるものではない。

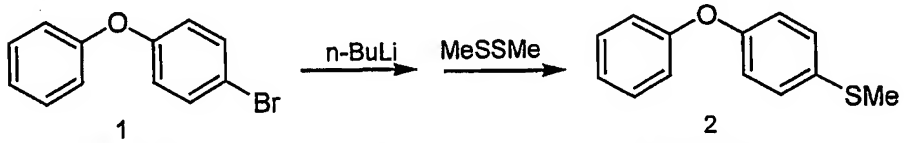
以下の実施例は本発明化合物の製造を示す。NMRデータはｐｐｍ(δ)で報告され、試料溶媒からのジュウテリウムのロック信号に対比したものである。市販の試薬はさらに精製せずに使用した。室温または周囲温度は２０℃から３０℃を表わす。非水性反応はすべて窒素雰囲気下で行われた。減圧下での濃縮は、回転蒸発器を用いたことを意味する。

得られた目的化合物は必要ならば、例えば再結晶、再沈殿、または、通常、有機化合物の分離精製に慣用されている方法、例えば、シリカゲル、アルミナ、マグネシウムーシリカゲル系のフロリジルのような担体を用いた吸着カラムクロマトグラフィー法；セファデックスＬＨ－２０(ファルマシア社製)、アンバーライトＸＡＤ－１１(ローム・アンド・ハース社製)、ダイヤイオンＨＰ－２０(三菱化学社製)のような担体を用いた分配カラムクロマトグラフィー等の合成吸着剤を使用する方法、イオン交換クロマトを使用する方法、または、シリカゲルもしくは低級アルキル化シリカゲルによる順相・逆相カラムクロマトグラフィー法(好適には、高速液体クロマトグラフィーである。)を適宜組合せ、適切な溶離剤で溶出することによって分離、精製することができる。

実施例１

４－(４－メチルスルホニルフェノキシ)フェニルスルホニルクロリドの合成

工程(i)

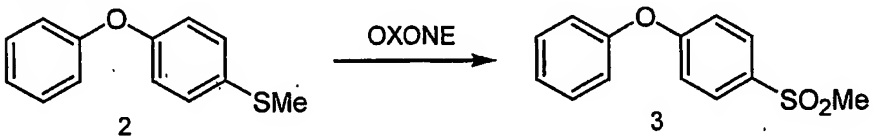


1 2

窒素雰囲気下の化合物１(69g)のＴＨＦ(350ml)溶液を内温－７０℃に冷却した。これにｎ－ブチルリチウムのヘキサン溶液(ｆ＝1.56、187ml)を内温－６５℃以下で滴下した。全量滴下したのち、１時間同温度で撹拌した。次いで、メチルジスルフィド(26.2ml)を内温－６０℃以下で滴下した。撹拌を続け、ゆっくりと室温に戻した。一晩撹拌後、反応系に水(50ml)を滴下し、反応を終了させた。反応

系を減圧濃縮し、塩化アンモニウム溶液と酢酸エチルから抽出した。油層を水洗後、硫酸ナトリウムで脱水し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン／酢酸エチル＝９／１)で精製し、化合物２(61.7g、淡黄色液体)を得た。

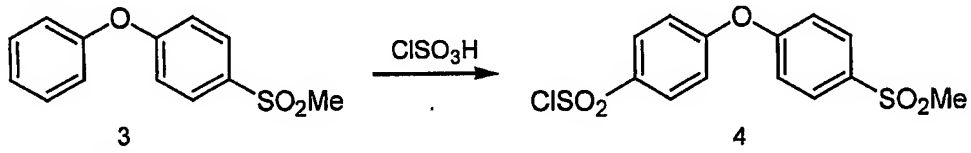
工程(ii)



2 3

化合物２(20g)、酢酸エチル(250ml)、メタノール(250ml)、水(200ml)の混合溶液にＯＸＯＮＥ(登録商標)(122g、アルドリッチ社)を小分けして加えた。３時間撹拌後、反応系に酢酸エチル(200ｍｌ)を加え、沈殿を濾別した。濾液を減圧濃縮後、水を加え、酢酸エチルで抽出した。油層を水洗後、硫酸ナトリウムで脱水、減圧濃縮した。得られた白色固体を減圧乾燥した。これを２回繰り返し、化合物３(46g)を得た。

工程(iii)



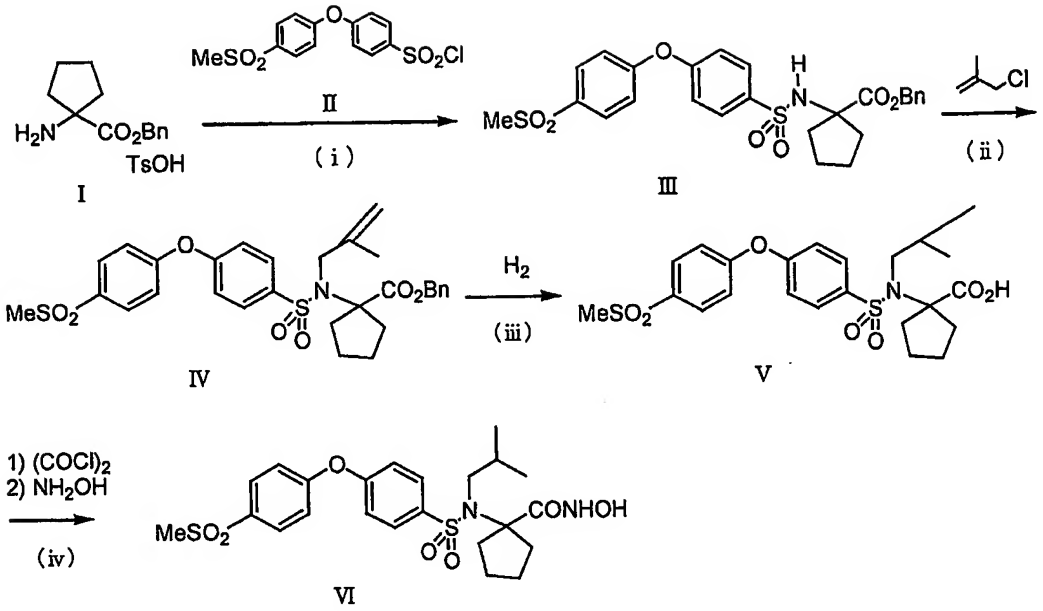
3 4

窒素雰囲気下にしたクロロ硫酸(60g)を氷冷下で撹拌した。これに化合物３(20グラム)を加え、自然に任せて室温に戻した。一晩撹拌後、反応系を氷水(500ml)に加えた。生成した白色固体を濾取し、水洗後、減圧乾燥し、白色固体化合物４(21g, 77%)を得た。

^{1}H-NMR(DMSO-D_6) δ 3.19(s, 3H), 7.09(m, 2H), 7.17(m, 2H), 7.67(m, 2H), 7.90(m, 2H)

実施例２

Ｎ－ヒドロキシ－1－[イソブチル({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]シクロペンタンカルボキサミドの合成



工程(i)

化合物I(37g)、ジイソプロピルエチルアミン(35ml)、ジメチルホルムアミド(400ml)を0℃で撹拌した。これに化合物II(33g)を小分けにして加えた。終夜撹拌で室温まで昇温した。塩酸水を加えた後、酢酸エチルで抽出した。油層を分離し、炭酸カリウム溶液、食塩水の順で洗浄し、硫酸ナトリウムで脱水し、減圧濃縮し、化合物III(37.6g)を得た。

工程(ii)

化合物III(37.6g)にジメチルホルムアミド(200ml)、塩化β-メタリル(8.36g)、炭酸カリウム(14.72g)、ヨウ化カリウム(1.18g)を加えた後、70℃で14時間撹拌した。室温に戻して、酢酸エチルと水を加えて抽出した。油層を食塩水で洗浄し、硫酸ナトリウムで脱水した後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒：ヘキサン/酢酸エチル=7/3から6/4)で精製し、化合物IV(38.2g)を得た。

工程(iii)

化合物IV(38.2g)に酢酸エチル(300ml)、5%パラジウム/炭素(2g)を加え、室温、常圧の水素雰囲気下で撹拌した。8時間後、触媒をセライト濾別し、減圧濃縮し、化合物V(32.1g)を得た。

工程(iv)

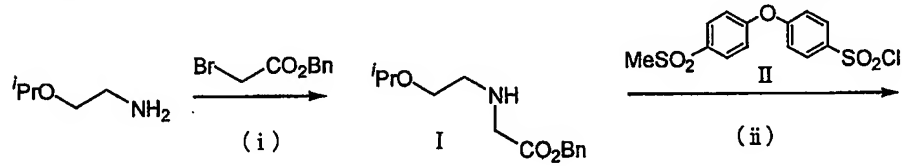
化合物V(32.1g)のジクロロメタン(400ml)溶液にジメチルホルムアミド(0.1g)

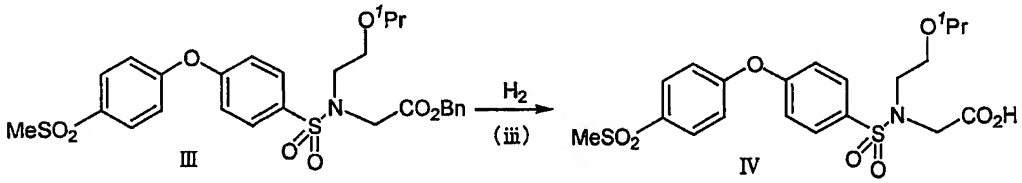
を加え、0℃で撹拌した。これにオギザリルクロリド(7.46ml)を加えた。1時間後、室温にして6時間撹拌した。減圧濃縮後、残渣にテトラヒドロフラン(250ml)を加えた。この溶液を、0℃で撹拌したヒドロキシルアミン塩酸塩(22.9g)、炭酸水素ナトリウム(38.8g)、テトラヒドロフラン(200ml)、水(20ml)の混合溶液に滴下した。反応溶液を減圧濃縮後、酢酸エチルと塩酸水を加えて、抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒：ヘキサン/酢酸エチル＝4/6から3/7)で精製し、化合物VI(32.4g)を得た。

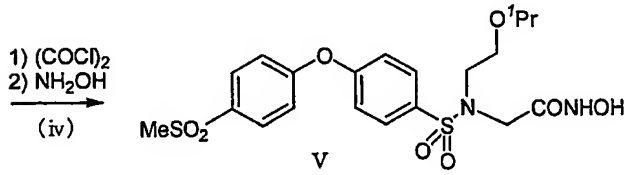
^{1}H-NMR(DMSO-D_6) δ 0.83(d, J=6.4Hz, 6H), 1.47(m, 2H), 1.57(m, 2H), 1.83(m, 2H), 1.95(m, 1H), 2.29(m, 2H), 3.18 (d, J=7.2Hz, 2H), 3.23(s, 3H), 7.24-7.33(m, 4H), 7.84(m, 2H), 7.97(m, 2H), 8.78(s, 1H), 10.30(s, 1H)

実施例3

N^1－ヒドロキシ-N^2－(2－イソプロポキシエチル)－N^2－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミドの合成







工程(i)

2-イソプロポキシエチルアミン(2.5g)、ジイソプロピルエチルアミン(4.22ml)、ジメチルホルムアミド(30ml)を0℃で撹拌し、ブロモ酢酸ベンジル(3.3ml)を滴下した。室温まで昇温し、8時間後酢酸エチルと食塩水から分液抽

出した。油層を硫酸ナトリウムで脱水し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒：ヘキサン/酢酸エチル＝1/4)で精製し、化合物Ｉ(4.3ｇ)を得た。

工程(ii)

0℃の化合物Ｉ(1g)、ジイソプロピルエチルアミン(1.4ml)、ジメチルホルムアミド(30ml)に対して、化合物II(1.4g)を小分けにして加えた。室温として１２時間後、酢酸エチルと塩酸水から分液抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒：ヘキサン/酢酸エチル＝1/1)で精製し、化合物III(1.5g)を得た。

工程(iii)

化合物III(1.47g)に酢酸エチル(30ml)、5%パラジウム/炭素(0.1g)を加えて、室温、常圧の水素雰囲気下で撹拌した。８時間後、触媒をセライト濾別し、減圧濃縮し、化合物IV(1.2g)を得た。

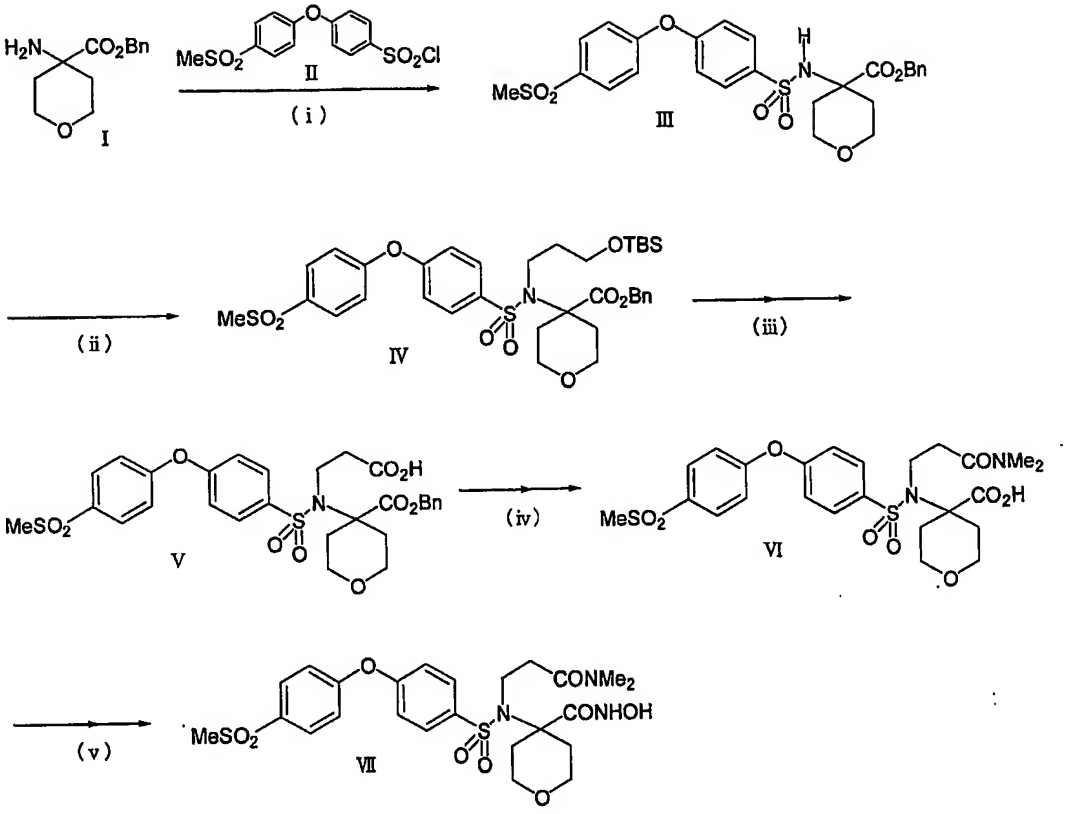
工程(iv)

化合物IV(1.19g)にジクロロメタン(20ml)、ジメチルホルムアミド(10mg)を加えた後、0℃でオギザリルクロリド(0.3ml)を加えた。室温で５時間撹拌後、減圧濃縮した。残渣にテトラヒドロフラン(15ml)を加えた。この溶液を0℃で撹拌したヒドロキシルアミン塩酸塩(0.9g)、炭酸水素ナトリウム(1.5g)、テトラヒドロフラン(20ml)、水(5ml)の混合溶液に滴下した。反応溶液を酢酸エチルと塩酸水を加えて、抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮した。残渣をクロロホルムから結晶化し、化合物V(0.8g)を得た。

^{1}H-NMR(DMSO-D_6) δ 1.02(d, J=6.0Hz, 6H), 3.23(s, 3H), 3.33(m, 2H), 3.48(m, 3H), 3.81(m, 2H), 7.26-7.33 (m, 4H), 7.90(m, 2H), 7.98(m, 2H), 8.90(s, 1H), 10.53(s, 1H)

実施例４

Ｎ－{４－[(ヒドロキシアミノ)カルボニル]テトラヒドロ－２Ｈ－ピラン－４－イル}－Ｎ－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニンジメチルアミドの合成



工程(i)

化合物I(4g)、ジイソプロピルエチルアミン(5.9ml)、テトラヒドロフラン(100ml)を0℃で撹拌し、これに化合物II(6.0g)を小分けにして加えた。4時間後反応系を減圧濃縮した。残渣を酢酸エチルと食塩水から抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮後、シリカゲルカラムクロマトグラフィー(溶出溶媒:ヘキサン/酢酸エチル=2/1、1/2)で精製し、化合物III(3.0g)を得た。

工程(ii)

0℃で撹拌した化合物III(3.0g)のジメチルホルムアミド(50ml)溶液に、カリウムヘキサメチルジシラジド(1.5g)を加えた。10分後、室温とした。更に90分後、3-(tert-ブチルジメチルシリル)オキシ-1-ヨードプロパン(2.12g)のジメチルホルムアミド溶液(5ml)を加えた。2日間撹拌後、酢酸エチルと食塩水から抽出した。硫酸ナトリウムで脱水後、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒:ヘキサン/酢酸エチル=2/1、1/2、0/1)で精製した。化合物IV(1.2g)を得た。また、同時に化合物IVの脱シリル体であるアルコール体(0.6g)を得た。

工程(iii)

化合物IV(1.17g)のジクロロメタン(50ml)溶液に対して、0℃でトリフロロボランジエチルエーテル錯体(0.43ml)を加えた。２時間後、０．５規定塩酸とクロロホルムで分液抽出した。硫酸ナトリウムで脱水後、減圧濃縮した。

この残渣に工程(ii)で得たアルコール体(0.6グラム)を加え、アセトン(40ml)を加えた。この溶液に、室温でJone's 試薬を反応系が橙色となるまで加えた。２０分後、沈殿をセライト濾別し、濾液を酢酸エチルと水で分液抽出した。油層を減圧濃縮後、トルエンと炭酸カリウム溶液から抽出した。水層を塩酸水で酸性とし、酢酸エチルで抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮し、化合物V(1.24g)を得た。

工程(iv)

－１５℃の化合物V(0.47g)、N-メチルモルホリン(0.25ml)、テトラヒドロフラン(30ml)溶液に、イソプロピルクロロホルメイト(0.1ml)を滴下した。１５分後、ジメチルアミンのテトラヒドロフラン溶液(２モル濃度、0.76ml)を滴下した。３０分後、塩酸水と酢酸エチルから分液抽出した。油層を硫酸ナトリウムで脱水し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(溶出溶媒：ヘキサン/酢酸エチル＝1/4)で精製した。精製したアミド体に、酢酸エチル(30ml)、５％パラジウム/炭素(80mg)を加えて、室温、常圧の水素雰囲気下で撹拌した。４時間後、触媒をセライト濾別し、減圧濃縮し、化合物VI(0.4g)を得た。

工程(v)

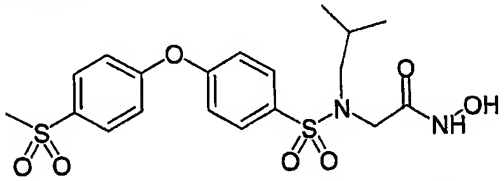
化合物VI(0.42ｇ)、ジイソプロピルアミン(0.15ml)のジメチルホルムアミド(10ml)溶液に、室温でＯ－(１Ｈ－ベンゾトリアゾール－１－イル)－Ｎ,Ｎ,Ｎ’,Ｎ’－テトラメチルーウロニウム　ヘキサフロロホスフェイト (HBTU、0.3g)を加えた。３時間後、ジイソプロピルアミン(0.3ml)、Ｏ－ベンジルヒドロキシルアミン塩酸塩(0.2ｇ)を加え、８０℃で１２時間撹拌した。室温に戻して、酢酸エチルと重曹水で分液抽出した。油層を塩酸水、食塩水の順で洗浄して、硫酸ナトリウムで脱水し、減圧濃縮後、シリカゲルカラムクロマトグラフィー(溶出溶媒：メタノール/酢酸エチル＝0/1、1/100)で精製した。精製物にテトラヒドロフラン(10ml)、メタノール(20ml)、５％パラジウム/炭素(0.1g)を加えて、室温、常圧の

水素雰囲気下で撹拌した。４時間後触媒をセライト濾別し、減圧濃縮し、化合物VII(0.1ｇ)を得た。

^{1}H-NMR(DMSO-D_6) δ 1.91(m, 2H), 2.29(m, 2H), 2.67(m, 2H), 2.79(s, 3H), 2.94(s, 3H), 3.23(s, 3H), 3.38 (t, J= 10.8Hz, 2H), 3.49(m, 2H), 3.71(m, 2H), 7.28(m, 2H), 7.33(m, 2H), 7.89(m, 2H), 7.98(m, 2H), 8.96(s, 1H), 10.69(s, 1H)

以下の実施例５－４８のうち、実施例５－７、９－２４、３２－３５、３７－３８、４１－４２、および４６－４８の化合物は実施例２と同様にして製造され、実施例８、３６、３９－４０、および４３－４４の化合物は実施例３と同様にして製造され、そして実施例２５－３１、および４５の化合物は実施例４と同様にして製造された。

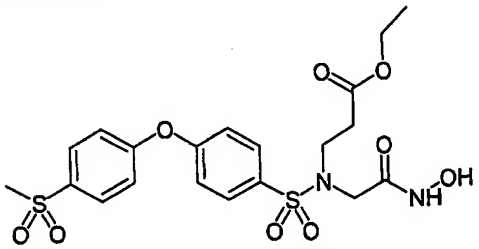
実施例５



N'^{1}-ヒドロキシ-N'^{2}-イソブチル-N'^{2}-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 0.82(d, J=6.8Hz, 6H), 1.85(m, 1H), 2.92(d, J=7.6Hz, 2H), 3.23(s, 3H), 3.71(s, 2H), 7.23-7.31(m, 4H), 7.87 (m, 2H), 7.97(m, 2H), 8.91(s, 1H), 10.58(s, 1H).

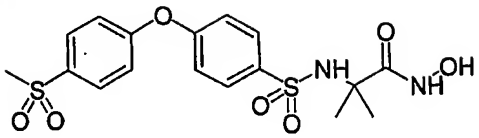
実施例６



エチルN－[２－(ヒドロキシアミノ)－２－オキソエチル]－N－({４-[４-(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニネイト

^{1}H-NMR(DMSO-D_6) δ 1.17(t, J=7.2Hz, 3H), 2.63(t, J=7.6Hz, 2H), 3.23(s, 3H), 3.41(t, J= 7.6Hz, 2H), 3.79(s, 2H), 4.04(q, J=7.2Hz, 2H), 7.23-7.34(m, 4H), 7.88(m, 2H), 7.98(m, 2H), 8.94(s, 1H), 10.62(s, 1H).

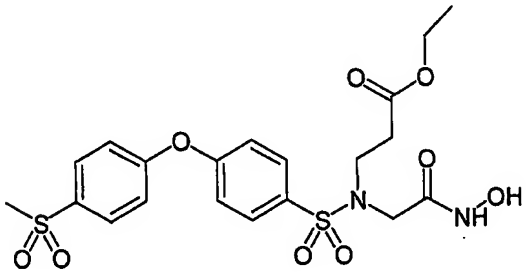
実施例７



N'$^{1'}$－ヒドロキシ－２－メチル－N'$^{2'}$－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アラニンアミド

^{1}H-NMR(DMSO-D_6) δ 1.25(s, 6H), 3.22(s, 3H), 7.25-7.31(m, 4H), 7.80(br, 1H), 7.88 (m, 2H), 7.96(m, 2H), 8.74(s, 1H), 10.40 (s, 1H).

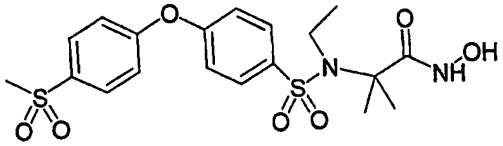
実施例８



エチルN－[２－(ヒドロキシアミノ)－２－オキソエチル]－N－({４－[４-(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニネイト

^{1}H-NMR(DMSO-D_6) δ 1.17(t, J=7.2Hz, 3H), 2.63(t, J=7.6Hz, 2H), 3.23(s, 3H), 3.41(t, J= 7.6Hz, 2H), 3.79(s, 2H), 4.04(q, J=7.2Hz, 2H), 7.23-7.34 (m, 4H), 7.88(m, 2H), 7.98(m, 2H), 8.94 (s, 1H), 10.62 (s, 1H).

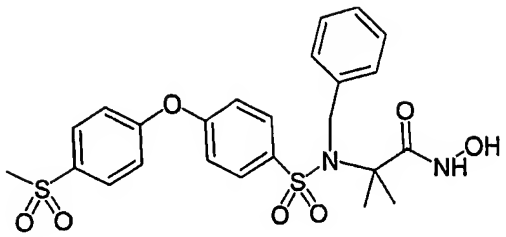
実施例９



N'$^{1'}$－ヒドロキシ－N'$^{2'}$－エチル－２－メチル－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アラニンアミド

^{1}H-NMR(DMSO-D_6) δ 1.12(t, J=6.8Hz, 3H), 3.19-3.24(m, 5H), 7.25-7.33 (m, 4H), 7.96-8.03(m, 4H), 8.76 (s, 1H), 10.39 (s, 1H).

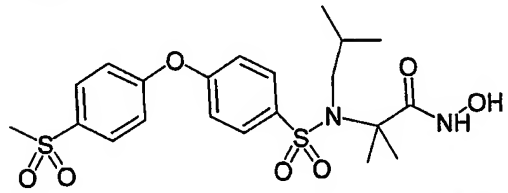
実施例１０



N'$^{2'}$－ベンジル－N'$^{1'}$－ヒドロキシ－２－メチル－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アラニンアミド

^{1}H-NMR(DMSO-D_6) δ 1.46(s, 6H), 3.23(s, 3H), 4.56(s, 2H), 7.17-7.24(m, 7H), 7.32(m, 2H), 7.94-7.99(m, 4H), 8.78(s, 1H), 10.41 (s, 1H).

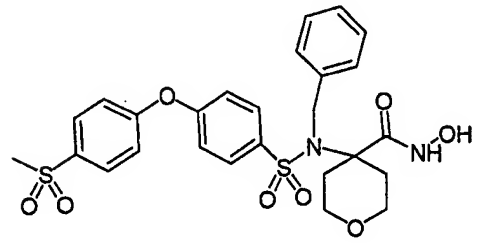
実施例１１



N'$^{1'}$－ヒドロキシ－N'$^{2'}$－イソブチル－２－メチル－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アラニンアミド

^{1}H-NMR(DMSO-D_6) δ 0.74(d, J=6.8Hz, 6H), 1.45(s, 6H), 1.86(m, 1H), 3.07(d, J=7.6Hz, 2H), 3.23(s, 3H), 7.25-7.30(m, 4H), 7.96-7.99(m, 4H), 8.75(s, 1H), 10.36 (s, 1H).

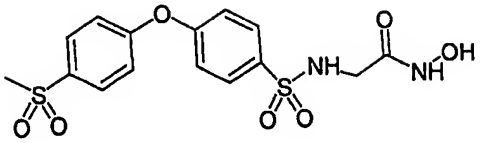
実施例１２



４－[ベンジル({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－N－ヒドロキシテトラヒドロ－２H－ピラン－４－カルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.82(m, 2H), 2.38(m, 2H), 3.23(s, 3H), 3.64(m, 2H), 4.68 (s, 2H), 7.22-7.39(m, 9H), 7.88(m, 2H), 7.97(m, 2H), 8.92(s, 1H), 10.68 (s, 1H).

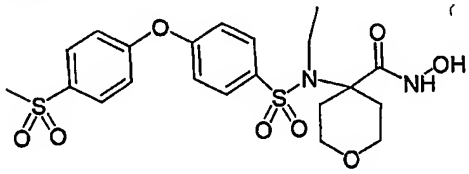
実施例１３



N'-ヒドロキシ-N'-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 3.26(s, 3H), 3.35(s, 2H), 7.28-7.32(m, 4H), 7.85(m, 2H), 7.96(m, 2H), 8.02(brs, 1H), 8.88(s, 1H), 10.56 (s, 1H).

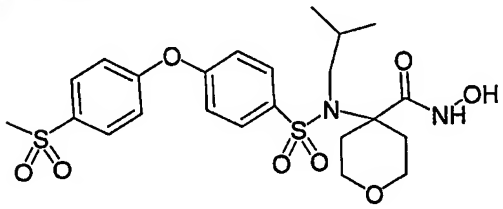
実施例14



4-[エチル({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-N-ヒドロキシテトラヒドロ-2H-ピラン-4-カルボキサアミド

^{1}H-NMR(DMSO-D_6) δ 1.16(t, J=6.8Hz, 3H), 1.90(m, 2H), 2.30(m, 2H), 3.23(s, 3H), 3.36(q, J=6.8Hz, 2H), 3.72(m, 2H), 7.26-7.35(m, 4H), 7.90(m, 2H), 7.97(m, 2H), 8.94(s, 1H), 10.65 (s, 1H).

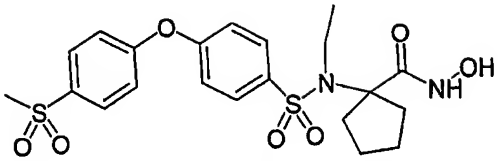
実施例15



N-ヒドロキシ-4-[イソブチル({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]テトラヒドロ-2H-ピラン-4-カルボキサミド

^{1}H-NMR(DMSO-D_6) δ 0.84(d, J=6.8Hz, 6H), 1.82-2.02(m, 3H), 2.27(m, 2H), 3.18-3.32(m, 7H), 3.72(m, 2H), 7.28-7.33(m, 4H), 7.85 (m, 2H), 7.98(m, 2H), 8.95(s, 1H), 10.65 (s, 1H).

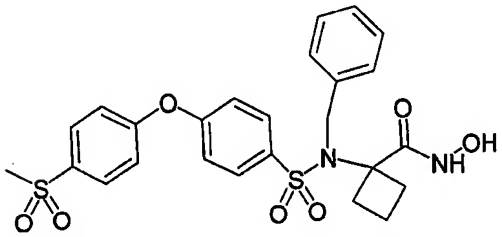
実施例16



1－[エチル({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－N－ヒドロキシシクロペンタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.15(t, J=7.2Hz, 6H), 1.47-1.62(m, 4H), 1.90(m, 2H), 2.30(m, 2H), 3.23(s, 3H), 3.37(q, J=7.2Hz, 2H), 7.25(m, 2H), 7.31(m, 2H), 7.90(m, 2H), 7.97(m, 2H), 8.77(s, 1H), 10.34 (s, 1H).

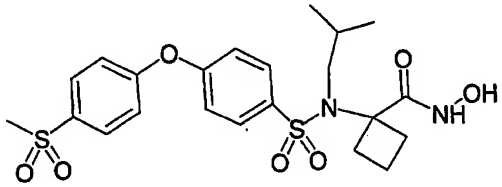
実施例17



1－[ベンジル({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－N－ヒドロキシシクロブタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.68(m, 2H), 2.40(m, 4H), 3.24(s, 3H), 4.56(m, 2H), 7.16(m, 2H), 7.27-7.36(m, 4H), 7.69(m, 2H), 7.97(m, 2H), 8.89(s, 1H), 10.80(s, 1H).

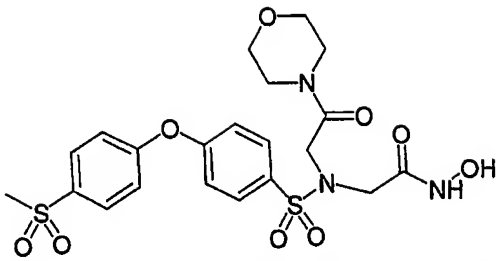
実施例18



N－ヒドロキシ－1－[イソブチル({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]シクロブタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 0.85(d, J=6.4Hz, 6H), 1.66(m, 2H), 1.89(m, 1H), 2.36(m, 4H), 2.97(d, J=7.6Hz, 2H), 3.23(s, 3H), 7.25(m, 2H), 7.32 (m, 2H), 7.82(m, 2H), 7.97(m, 2H), 8.88(s, 1H), 10.58(s, 1H).

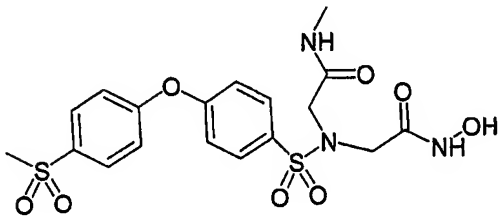
実施例19



N－{１－[(ヒドロキシアミノ)カルボニル]メチル}－N－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)-グリシン モルホリノアミド

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 3.41(m, 4H), 3.56(m, 4H), 3.81(s, 2H), 4.29(s, 2H), 7.26-7.32(m, 4H), 7.91 (m, 2H), 7.97(m, 2H), 8.90(s, 1H), 10.90(s, 1H).

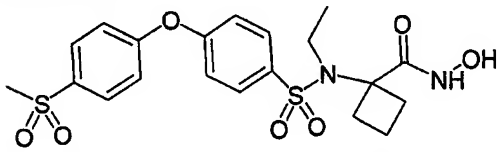
実施例２０



N'$^{1'}$－ヒドロキシ－N'$^{2'}$－[2－(メチルアミノ)－２－オキソエチル]－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 2.60(d, J=4.4Hz, 3H), 3.23(s, 3H), 3.83(s, 2H), 3.85(s, 2H), 7.32(m, 4H), 7.89 (m, 2H), 7.98(m, 2H), 8.54(br, 1H), 9.03(s, 1H), 11.09(s, 1H).

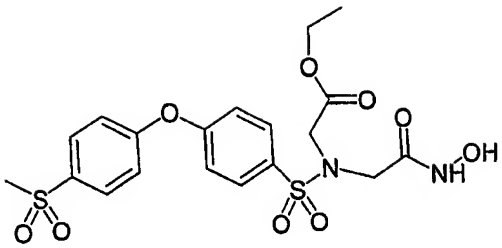
実施例２１



１－[エチル({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－N－ヒドロキシシクロブタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.15(t, J=7.2Hz, 3H), 1.69(m, 2H), 2.40(m, 4H), 3.23(s, 3H), 3.26(q, J=7.2Hz, 2H), 7.24(m, 2H), 7.32 (m, 2H), 7.842(m, 2H), 7.97(m, 2H), 8.87(s, 1H), 10.59(s, 1H).

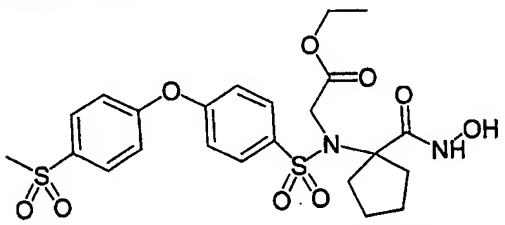
実施例２２



エチルN－{[(ヒドロキシアミノ)カルボニル]メチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－グリシネイト

^{1}H-NMR(DMSO-D_6) δ 1.14(t, J=7.2Hz, 3H), 3.23(s, 3H), 3.86(s, 2H), 4.04(q, J=7.2Hz, 2H), 4.17(s, 2H), 7.26-7.32 (m, 4H), 7.89(m, 2H), 7.98(m, 2H), 8.94 (s, 1H), 10.61(s, 1H).

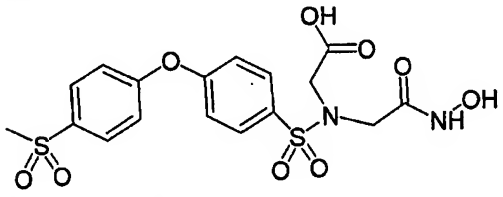
実施例２３



エチルN－{1－[(ヒドロキシアミノ)カルボニル]シクロペンチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシネイト

^{1}H-NMR(DMSO-D_6) δ 1.17(t, J=7.2Hz, 3H), 1.53(m, 4H), 1.89(m, 2H), 2.23(m, 2H), 3.23(s, 3H), 4.02(q, J=7.2Hz, 2H), 4.29(s, 2H), 7.26 (m, 2H), 7.31(m, 2H), 7.92(m, 2H), 7.98(m, 2H), 8.87(s, 1H), 10.42(s, 1H).

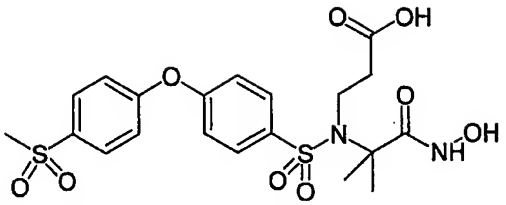
実施例２４



N－{[(ヒドロキシアミノ)カルボニル]メチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－グリシン

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 3.88(s, 2H), 4.07(s, 2H), 7.26-7.32(m, 2H), 7.90(m, 2H), 7.97(m, 2H), 8.99+9.24 (s, 1H), 10.23+10.70(s, 1H), 13.02(br, 1H).

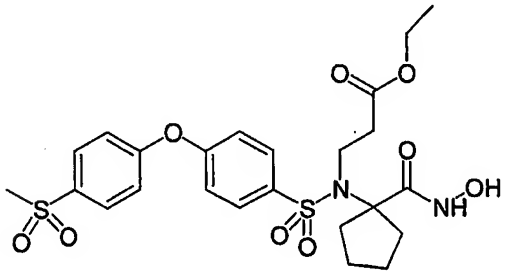
実施例２５



N－{[(ヒドロキシアミノ)カルボニル]－ジメチルメチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニン

^{1}H-NMR(DMSO-D_6) δ 1.46(s, 6H), 2.60(m, 2H), 3.23(s, 3H), 3.38(m, 2H), 7.26-7.34 (m, 4H), 7.96-8.00(m, 4H), 8.80(s, 1H), 10.41 (s, 1H), 12.31(brs, 1H).

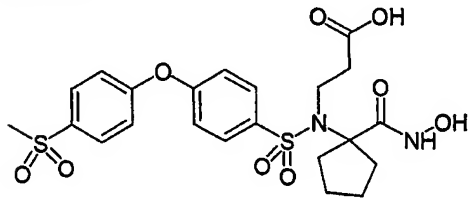
実施例２６



エチルN－{1－[(ヒドロキシアミノ)カルボニル]シクロペンチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニネイト

^{1}H-NMR(DMSO-D_6) δ 1.18(t, J=7.2Hz, 3H), 1.55(m, 4H), 1.89(m, 2H), 2.26(m, 2H), 2.71(m, 2H), 3.23(s, 3H), 3.54(m, 2H), 4.05(q, J=7.2Hz, 2H), 7.26-7.34 (m, 4H), 7.89(m, 2H), 7.98(m, 2H), 8.80 (s, 1H), 10.43(s, 1H).

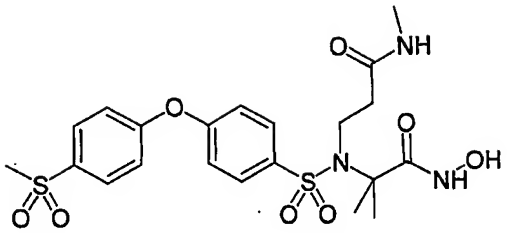
実施例２７



N－{1－[(ヒドロキシアミノ)カルボニル]シクロペンチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニン

^{1}H-NMR(DMSO-D_6) δ 1.56(m, 4H), 1.90(m, 2H), 2.26(m, 2H), 2.63(m, 2H), 3.23(s, 3H), 3.50(m, 2H), 4.05(q, J=7.2Hz, 2H), 7.27(m, 4H), 7.32(m, 4H), 7.89(m, 2H), 7.98(m, 2H), 8.80 (s, 1H), 10.44(s, 1H), 12.31 (brs, 1H).

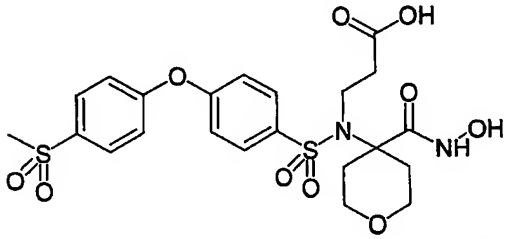
実施例２８



N'-[2-(ヒドロキシアミノ)-2-オキソ-1,1-ジメチルエチル]-N'-メチル-N'-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-β-アラニンアミド

^{1}H-NMR(DMSO-D_6) δ 1.47(s, 6H), 2.45(s, 3H), 2.55(m, 2H), 3.23(s, 3H), 3.37(m, 2H), 7.26-7.35 (m, 4H), 7.82(m, 1H), 7.97-8.00(m, 4H), 8.77 (s, 1H), 10.43 (s, 1H).

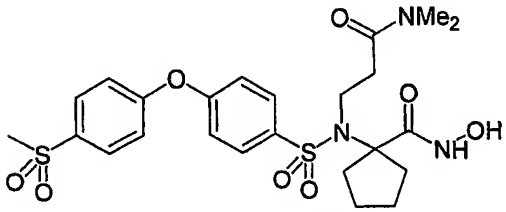
実施例29



N-{4-[(ヒドロキシアミノ)カルボニル]テトラヒドロ-2H-ピラン-4-イル}-N-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-β-アラニン

^{1}H-NMR(DMSO-D_6) δ 1.89(m, 2H), 2.28(m, 2H), 2.62(m, 2H), 3.23(s, 3H), 3.37(m, 2H), 3.50(m, 2H), 3.71(m, 2H), 7.26-7.39(m, 4H), 7.90(m, 2H), 7.98(m, 2H), 8.97(s, 1H), 10.69(s, 1H), 12.28(brs, 1H).

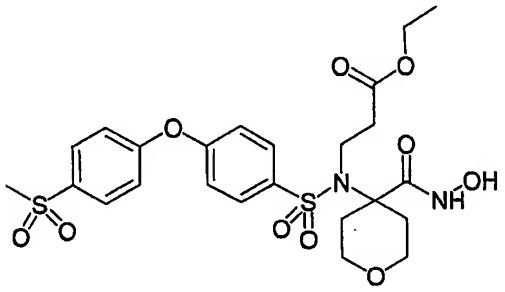
実施例30



N-{1-[(ヒドロキシアミノ)カルボニル]シクロペンチル}-N-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-β-アラニン ジメチルアミド

^{1}H-NMR(DMSO-D_6)1.55(m, 4H), 1.89(m, 2H), 2.28(m, 2H), 2.69(m, 2H), 2.78(s, 3H), 2.93(s, 3H), 3.23(s, 3H), 3.48(m, 2H), 7.26 (m, 2H), 7.32(m, 2H), 7.88m, 2H), 7.98(m, 2H), 8.76(s, 1H), 10.36(s, 1H).

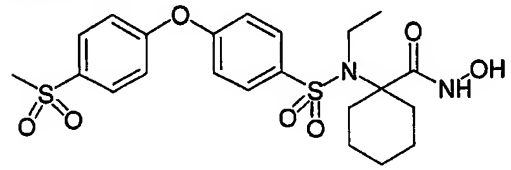
実施例３１



エチル Ｎ－{４－[(ヒドロキシアミノ)カルボニル]テトラヒドロ－２Ｈ－ピラン－４－イル}－Ｎ－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニネイト

^{1}H-NMR(DMSO-D_6)1.19(t, J=6.82Hz, 3H), 1.88(m, 2H), 2.28(m, 2H), 2.69(m, 2H), 3.23(s, 3H), 3.36(m, 2H), 3.53(m, 2H), 3.70(m, 2H), 4.05(q, J=6.8/Hz, 2H), 7.27-7.35(m, 4H), 7.90m, 2H), 7.98(m, 2H), 8.97(s, 1H), 10.69(s, 1H).

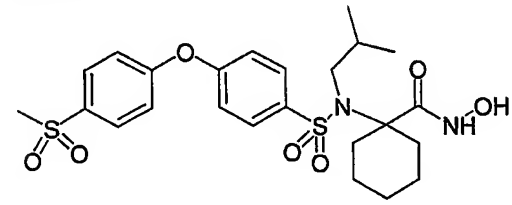
実施例３２



１－[エチル({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－Ｎ－ヒドロキシシクロヘキサンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ1.12(m, 1H), 1.15(t, J=6.8Hz, 3H), 1.35(m, 2H), 1.50(m, 3H), 1.68(m, 2H), 2.28(m, 2H), 3.23(s, 3H), 3.32(q, J=6.8Hz, 2H), 7.26(m, 2H), 7.31(m, 2H), 7.90(m, 2H), 7.98(m, 2H), 8.80(s, 1H), 10.53(s, 1H).

実施例３３

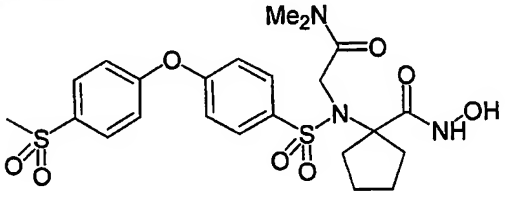


Ｎ－ヒドロキシ－１－[イソブチル({４－[４－(メチルスルホニル)フェノキシ]

フェニル}スルホニル)アミノ] シクロヘキサンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 0.82(d, J=6.8Hz, 1H), 1.04(m, 1H), 1.27(m, 2H), 1.50(m, 3H), 1.66(m, 2H), 1.98(m, 1H), 2.26(m, 2H), 3.18(d, J=7.2Hz, 2H), 3.23(s, 3H), 7.42-7.31(m, 4H), 7.86(m, 2H), 7.98(m, 2H), 8.82(s, 1H), 10.57(s, 1H).

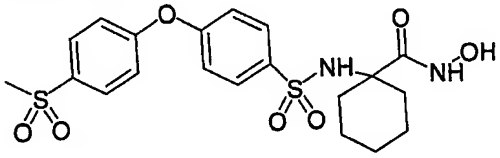
実施例３４



N－{１－[(ヒドロキシアミノ)カルボニル]シクロペンチル}－N－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－グリシンジメチルアミド

^{1}H-NMR(DMSO-D_6) δ 1.55(m, 4H), 1.82(m, 2H), 2.14(m, 2H), 2.79(s, 3H), 2.99(s, 3H), 3.33(s, 3H), 4.29(s, 2H), 7.22-7.31(m, 4H), 7.94-8.00(m, 4H), 8.79(s, 1H), 11.64(s, 1H).

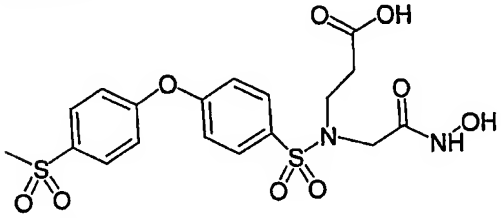
実施例３５



Ｎ－ヒドロキシ－１－[({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]シクロヘキサンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.28(m, 6H), 1.65(m, 2H), 1.78(m, 2H), 3.22(s, 3H), 7.25-7.33(m, 4H), 7.59(s, 1H), 7.84(m, 2H), 7.95(m, 2H), 8.62(s, 1H), 10.25(s, 1H).

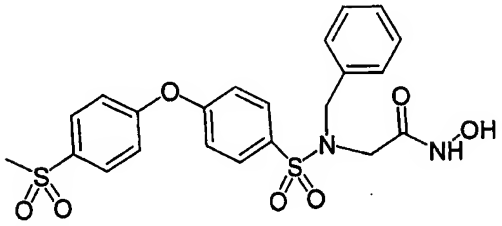
実施例３６



Ｎ－[２－(ヒドロキシアミノ)－２－オキソエチル]－Ｎ－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニン

^{1}H-NMR(DMSO-D_6) δ 2.55(t, J=7.6Hz, 2H), 3.23(s, 3H), 3.41(t, J=7.6Hz, 2H), 3.79(s, 2H), 7.28-7.34(m, 4H), 7.88(m, 2H), 7.98(m, 2H), 8.92(s, 1H), 10.63(s, 1H), 12.37(brs, 1H).

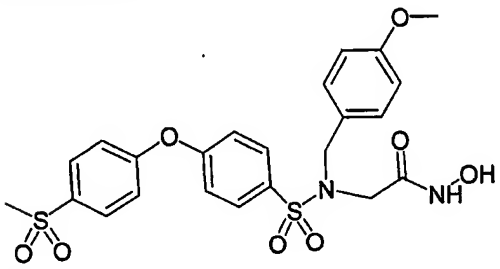
実施例３７



N'$^{2'}$－ベンジル－N'$^{1'}$－ヒドロキシ－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 3.67(s, 2H), 4.34(s, 2H), 7.24-7.36(m, 9H), 7.93(m, 2H), 7.99(m, 2H), 8.89(s, 1H), 10.53(s, 1H).

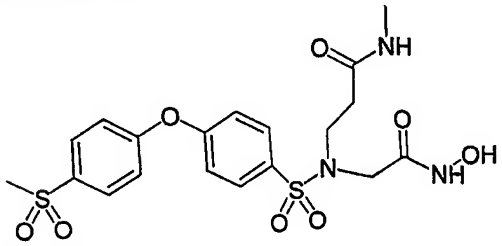
実施例３８



N'$^{1'}$－ヒドロキシ－N'$^{2'}$－(４－メトキシベンジル)－N'$^{2'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 3.63(s, 2H), 3.73(s, 2H), 4.35(s, 2H), 6.89(m, 2H), 7.16(m, 2H), 7.27(m, 2H), 7.31(m, 2H), 7.92(m, 2H), 7.98(m, 2H), 8.88(s, 1H), 10.52(s, 1H).

実施例３９

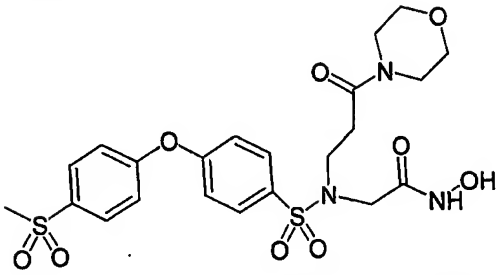


N'$^{3'}$－[２－(ヒドロキシアミノ)－２－オキソエチル]－N'$^{1'}$－メチル－N'$^{3'}$－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－β－アラニ

ンアミド

^{1}H-NMR(DMSO-D_6) δ 2.40(t, J=7.6Hz, 2H), 2.54(d, J=4.4Hz, 3H), 3.23(s, 3H), 3.76(s, 2H), 7.28-7.35(m, 4H), 7.88(m, 3H), 7.98(m, 2H), 8.94 (s, 1H), 10.68 (s, 1H).

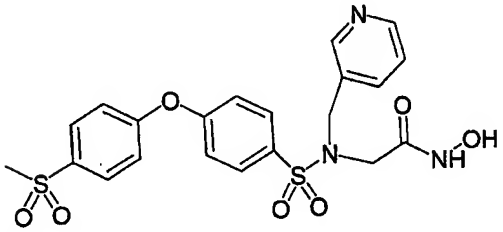
実施例４０



N-{1-[(ヒドロキシアミノ)カルボニル]メチル}-N-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-β-アラニンモルホリノアミド

^{1}H-NMR(DMSO-D_6) δ 2.66(m, 2H), 3.23(s, 3H), 3.38(m, 6H), 3.51-3.58(m, 4H), 3.81(s, 2H), 7.28-7.43(m, 4H), 7.88(m, 2H), 7.98(m, 2H), 8.93(s, 1H), 10.66(s, 1H).

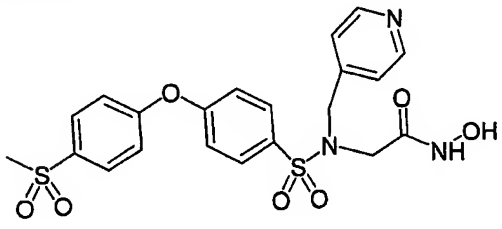
実施例４１



N'^{1}-ヒドロキシ-N'^{2}-({4-[4-(メチルスルホニル)フェノキシ]フェニル}スルホニル)-N'^{2}-(3-ピリジニルメチル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 3.73(s, 2H), 4.45(s, 2H), 7.26-7.36(m, 4H), 7.37(m, 1H), 7.71(m, 1H), 7.89(m, 2H), 7.99(m, 2H), 8.43(m, 1H), 7.49(m, 1H), 8.92(s, 1H), 10.59(s, 1H).

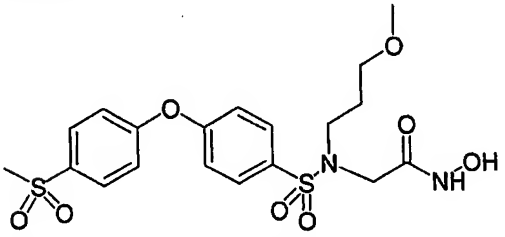
実施例４２



N'$^{1'}$－ヒドロキシ－N'$^{2'}$－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－N'$^{2'}$－(４－ピリジニルメチル)グリシナミド

^{1}H-NMR(DMSO-D_6) δ 3.23(s, 3H), 4.04(s, 2H), 4.685(s, 2H), 7.29-7.35(m, 4H), 7.85(br, 2H), 7.94-8.01(m, 4H), 7.72-8.79(br, 3H), 12.30(s, 1H).

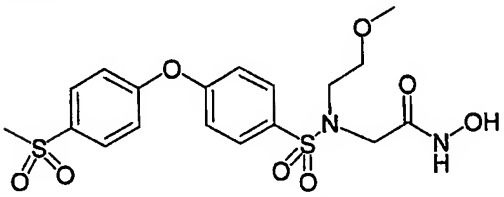
実施例４３



N^1－ヒドロキシ－N^2－(３－メトキシプロピル)－N^2－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシンアミド

^{1}H-NMR(DMSO-D_6) δ 1.70(m, 4H), 3.16-3.21(m, 5H), 3.23(s, 3H), 3.29(t, J=6.0Hz, 2H), 3.73(s, 2H), 7.27-7.34(m, 4H), 7.88(m, 2H), 7.98(m, 2H), 8.93(s, 1H), 10.62(s, 1H).

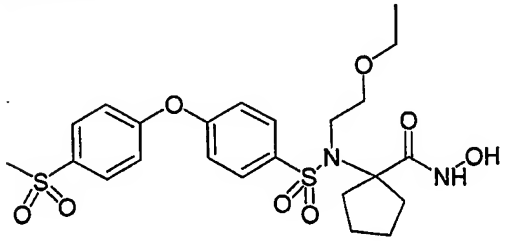
実施例４４



N^1－ヒドロキシ－N^2－(２－メトキシエチル)－N^2－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシンアミド

^{1}H-NMR(DMSO-D_6) δ 3.19(s, 3H), 3.23(s, 3H), 3.36(t, J=6.0Hz, 2H), 3.45(t, J=6.0Hz, 2H), 3.80(s, 2H), 7.23-7.33 (m, 4H), 7.89(m, 2H), 7.98(m, 2H), 8.91(s, 1H), 10.53(s, 1H).

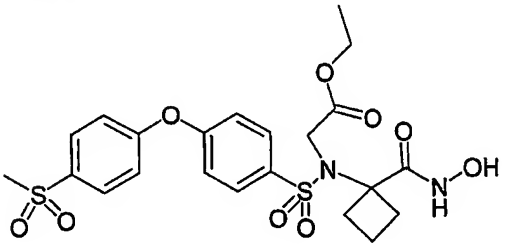
実施例４５



1－[(2－エトキシエチル)({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]－N－ヒドロキシシクロペンタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.09(t, J=6.8Hz, 3H), 1.53(m, 4H), 1.95(m, 2H), 2.24(m, 2H), 3.23(s, 3H), 3.39-3.49(m, 4H), 3.52(m, 2H), 3.81(m, 2H), 7.25-7.34(m, 4H), 7.90(m, 2H), 7.98(m, 2H), 8.81(s, 1H), 10.32(s, 1H).

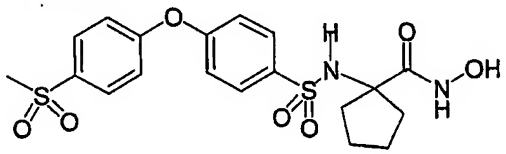
実施例46



エチルN－{1－[(ヒドロキシアミノ)カルボニル]シクロブチル}－N－({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)グリシネイト

^{1}H-NMR(DMSO-D_6) δ 1.18(t, J=7.2Hz, 3H), 1.69(m, 2H), 2.36(m, 4H), 3.23(s, 3H), 4.10(q, J=7.2Hz, 2H), 4.17(s, 2H), 7.25(m, 2H), 7.31(m, 4H), 7.84(m, 2H), 7.97(m, 2H), 8.88(s, 1H), 10.64(s, 1H).

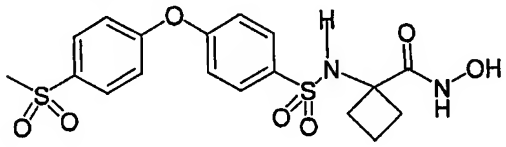
実施例47



N－ヒドロキシー1－[({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]シクロペンタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.27(m, 2H), 1.41(m, 2H), 1.79(m, 4H), 3.17(s, 3H), 7.19-7.22(m, 4H), 7.76(br, 1H), 7.79(m, 2H), 7.89(m, 2H), 8.64(s, 1H), 10.21(s, 1H).

実施例48

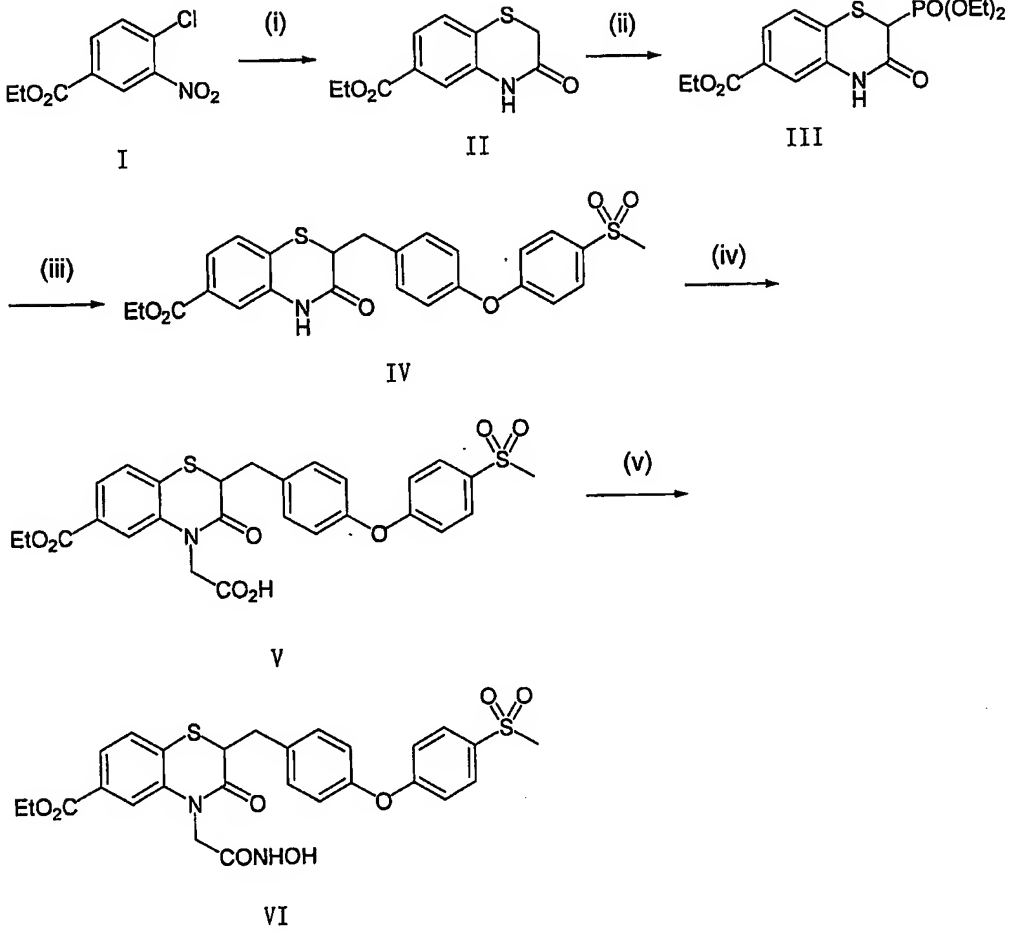


N－ヒドロキシー1－[({4－[4－(メチルスルホニル)フェノキシ]フェニル}スルホニル)アミノ]シクロブタンカルボキサミド

^{1}H-NMR(DMSO-D_6) δ 1.64(m, 2H), 2.05(m, 2H), 2.29(m, 4H), 3.23 (s, 3H), 7.26-

7.31(m, 4H), 7.84(m, 2H), 7.96(m, 2H), 8.21(br, 1H), 8.71(br, 1H),
10.41(s, 1H).

実施例４９



工程(ｉ)：

チオグリコール酸(10.8g)、炭酸カリウム(65g)、ジメチルホルムアミド(300ml)の混合物に、４－クロロ－３－ニトロ安息香酸エチル(28.1g)のＤＭＦ(100ml)溶液を加え、８０℃に加熱した。混合物を６時間で撹拌した後、固体を濾別し、濾液を減圧濃縮した。残渣にジエチルエーテル(50ml)と水(100ml)とを加え、黄色固体を濾取した。この固体を４Ｎ－塩酸を加えて酸性にし、酢酸エチルで抽出した。有機層を硫酸ナトリウムで乾燥、濃縮した。取得物(27.63g)はこのままで次反応に用いた。

先の取得物(12.9g)のテトラヒドロフラン(300ml)溶液に、１０% Pd/C (13g)を加え、室温、水素雰囲気下で９時間激しく撹拌した。触媒を濾別し、濾液を減

圧濃縮した。粗生成物(9.4ｇ)とN-ヒドロキシベンズトリアゾール(HOBt)(5.9g)とのジメチルホルムアミド(200ml)溶液に、１－エチル－３－(３－ジメチルアミノプロピル)カルボジイミド・塩酸塩(EDC・HCl)(7.4g)を加えた。室温で一夜撹拌し、減圧濃縮した。残渣を酢酸エチルに溶解し、１N-塩酸、５％炭酸ナトリウム水および食塩水の順で洗浄した。有機層を硫酸ナトリウムで乾燥、濃縮した。残渣をジエチルエーテルとヘキサンとから再結晶して精製し、化合物II(8.5g)を白色固体として得た。

工程(ii)：

化合物II(8.43g)のジクロロメタン(80ml)溶液に、塩化スルフリル(4.８グラム)を滴下した。室温で６時間撹拌し、減圧濃縮した。残渣をクロロホルムとヘキサンとから再結晶し、白色固体(8.8g)を得た。

取得した白色固体(8.7グラム)とトリエチルホスファイト(11.7グラム)の混合物を１２０℃で１０時間撹拌した。溶媒を減圧除去し、残渣をテトラヒドロフランとジエチルエーテルから再結晶し、化合物III(10.5g)を薄黄色固体として得た。

工程(iii)：

氷冷した窒素雰囲気下の４－(４－メチルスルホニルフェノキシ)ベンズアルデヒド(1.5g)と化合物III(1.9g)のテトラヒドロフラン(80ml)溶液に、６０％水素化ナトリウム(0.5g)を加えた。４時間後、反応系を減圧濃縮した。残渣に酢酸エチル(10ml)とヘキサン(50ml)を加えた後、１Ｎ－塩酸(20ml)、水(80ml)の順に加え、更にヘキサン(100ml)を加え、室温で２０分撹拌した。固体生成物を濾取し、減圧乾燥し、黄色固体(2.6g)を得た。

黄色固体(2.6g)にジオキサン(300ml)、メタノール(50ml)、テトラヒドロフラン(80ml)、および５％ Ｐｄ／Ｃ (2.6g)を加えた。常圧の水素雰囲気下、室温で６時間撹拌した。触媒を濾別し、濾液を減圧濃縮した。白色固体の化合物IV(2.3g)を得た。

工程(iv)：

氷冷した窒素雰囲気下の化合物IV(2.3g)のジメチルホルムアミド(20ml)溶液に、６０％水素化ナトリウム(0.2g)を加えた後、室温で１時間撹拌した。再び氷冷下として、ブロモ酢酸ｔ－ブチル(1ml)を滴下した。６時間後、塩化アンモニウム溶

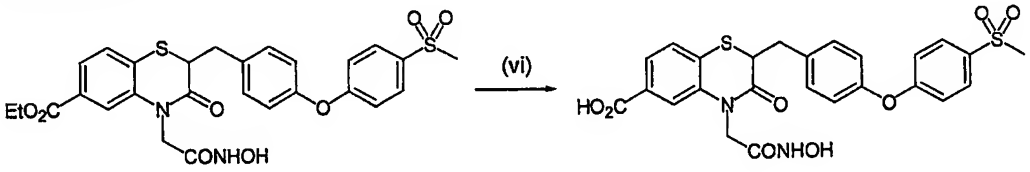
液に注ぎ、酢酸エチルで抽出した。有機層を硫酸ナトリウムで乾燥し、減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン/酢酸エチル=3/1から7/3)で処理し、付加体(2.4g)を得た。これに塩化メチレン(15ml)、1,2-エタンジチオール(0.8ml)を加え、0℃として、トリフロロ酢酸(20ml)を加えた。3時間後減圧濃縮した。ジイソプロピルエーテル(20ml)、ヘキサン(200ml)を加えて、出た固体を濾取乾燥し、化合物V(2.4g)を得た。

工程(v):

-15℃の窒素雰囲気下の化合物V(2.4g)、N-メチルモルホリン(0.6ml)のテトラヒドロフラン溶液(50ml)に、イソプロピルクロロホルメイト(0.5ml)を滴下した。20分後、O-トリメチルシリルヒドロキシルアミン(0.7ml)を滴下した。室温まで、ゆっくりと昇温して、1N-塩酸と酢酸エチルから抽出した。有機層を硫酸ナトリウムで乾燥し減圧濃縮した。残渣をシリカゲルカラムクロマトグラフィー(ヘキサン/酢酸エチル=1/1から1/4)で処理し、化合物VI(1.9g)を得た。

^{1}H-NMR($CDCl_3$) δ 1.41(t, J=7.2Hz, 3H), 2.88(m, 1H), 3.06(m, 1H), 3.20(m, 1H), 3.75(m, 1H), 4.40(q, J=7.2Hz, 2H), 4.50(d, J=16Hz, 1H), 4.74(d, J=16Hz, 1H), 7.00(m, 2H), 7.08(m, 1H), 7.18(m, 2H), 7.45(d, J=8.0Hz, 1H), 7.78(d, J=8.0Hz, 1H), 7.89(m, 2H) 8.09(m, 1H), 9.03(br, 1H)

実施例50



VI VII

0℃の実施例49の化合物(VI)(0.5g)のテトラヒドロフラン溶液(8ml)に0.5N水酸化リチウム水溶液(3.5ml)を滴下した。ゆっくりと室温に戻し、1晩撹拌した。3N-塩酸(70ml)を加え、酢酸エチル(80ml x 2)で抽出し、油層を硫酸ナトリウムで乾燥し、減圧濃縮した。テトラヒドロフラン-ヘキサンから再結晶し、化合物VII(0.4g)を得た。

^{1}H-NMR(DMSO-D_6) δ 2.81(m, 1H), 3.19(S, 3H), 3.40(m, 1H), 4.02(m, 1H), 4.52+4.73+4.95(2H, NCH2CO), 7.06(m, 2H), 7.13(m, 2H), 7.33(m, 2H), 7.51(d, J=8Hz, 1H), 7.62(dd, J=1.6, 8Hz, 1H), 7.67(d, J=1.6Hz, 1H), 7.91(m, 2H),

9.05+9.46(s, 1H), 10.41+10.85(s, 1H), 13.19(br, 1H)

下表１に挙げた実施例５１－５８の化合物は前記(製造法２及び製造法４)の方法で製造される。

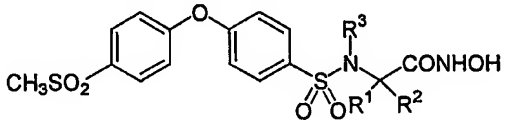


表１

実施例	R^1	R^2	R^3
５１	$-(CH_2)_4-$		$CH_2CH_2CH_3$
５２	$-(CH_2)_4-$		$CH(CH_3)CH_2CH_3$
５３	$-(CH_2)_3-$		$CH_2CH_2CH_3$
５４	$-(CH_2)_3-$		$CH(CH_3)CH_2CH_3$
５５	$-(CH_2)_3-$		CH_2COOH
５６	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2CH_3$
５７	$-(CH_2)_2-O-(CH_2)_2-$		$CH(CH_3)CH_2CH_3$
５８	H	$CH(CH_3)_2$	CH_2COOH

下表２に挙げた実施例５９－８０の化合物は前記(製造法４)の方法で製造される。

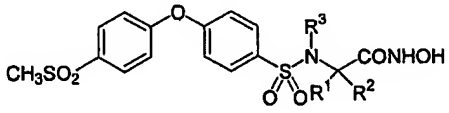
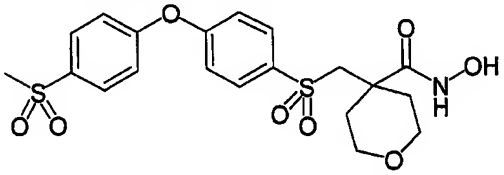


表２

実施例	R^1	R^2	R^3
５９	$-(CH_2)_4-$		$CH_2CH_2OCH(CH_3)_2$
６０	$-(CH_2)_4-$		$CH_2CH_2CH_2OCH_3$
６１	$-(CH_2)_4-$		$CH(CH_3)_2$
６２	$-(CH_2)_4-$		$CH_2CH_2OCH_3$
６３	$-(CH_2)_4-$		$CH_2CH_2CH_2OCH(CH_3)_2$
６４	$-(CH_2)_3-$		$CH_2CH_2OCH_2CH_3$

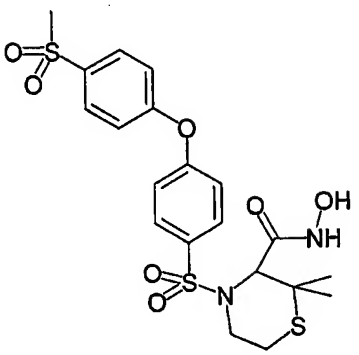
65	$-(CH_2)_3-$		$CH_2CH_2OCH(CH_3)_2$
66	$-(CH_2)_3-$		$CH_2CH_2CH_2OCH_3$
67	$-(CH_2)_3-$		$CH(CH_3)_2$
68	$-(CH_2)_3-$		$CH_2CH_2OCH_3$
69	$-(CH_2)_3-$		$CH_2CH_2CH_2OCH(CH_3)_2$
70	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2OCH_2CH_3$
71	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2OCH(CH_3)_2$
72	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2CH_2OCH_3$
73	$-(CH_2)_2-O-(CH_2)_2-$		$CH(CH_3)_2$
74	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2OCH_3$
75	$-(CH_2)_2-O-(CH_2)_2-$		$CH_2CH_2CH_2OCH(CH_3)_2$
76	H	$CH(CH_3)_2$	$CH_2CH_2OCH_2CH_3$
77	H	$CH(CH_3)_2$	$CH_2CH_2OCH(CH_3)_2$
78	H	$CH(CH_3)_2$	$CH_2CH_2CH_2OCH_3$
79	H	$CH(CH_3)_2$	$CH_2CH_2OCH_3$
80	H	$CH(CH_3)_2$	$CH_2CH_2CH_2OCH(CH_3)_2$

前記(製造法８)の方法に従い、下記化合物を製造することができる。



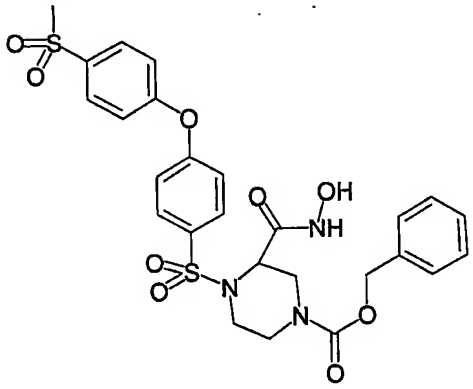
Ｎ－ヒドロキシ－４－[({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)メチル]テトラヒドロ－２Ｈ－ピラン－４－カルボキサミド。

前記(製造法９)の方法に従い、下記化合物を製造することができる。



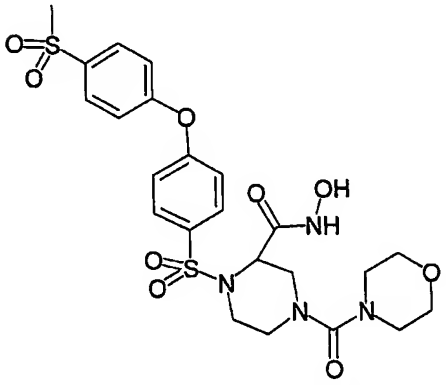
N－ヒドロキシ－２，２－ジメチル－４－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)チオモルホリン－３－カルボキサミド。

前記(製造法１１)の方法に従い、下記化合物を製造することができる。



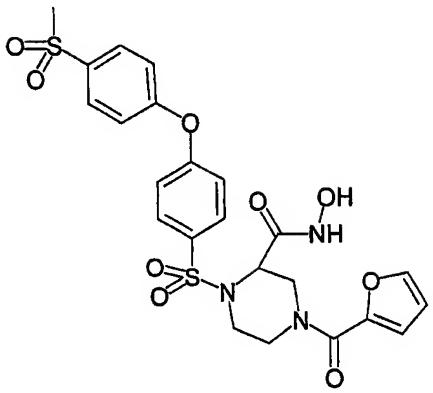
ベンジル ３－[(ヒドロキサミノ)カルボニル]－４－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)ピペラジン－１－カルボキシレート。

前記(製造法１１)の方法に従い、下記化合物を製造することができる。



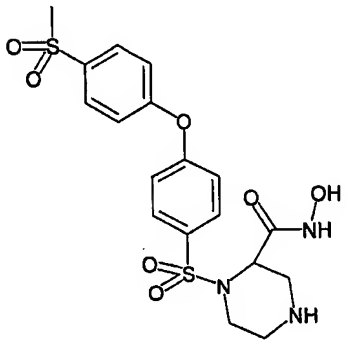
N－ヒドロキシ－１－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)－４－(モルホリン－４－イルカルボニル)ピペラジン－２－カルボキサミド。

前記(製造法１１)の方法に従い、下記化合物を製造することができる。



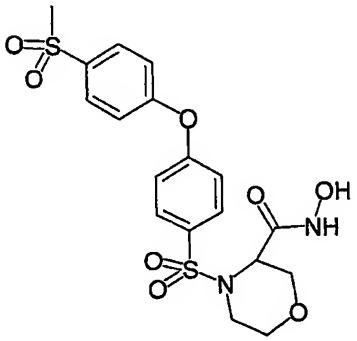
４－(２－フロイル)－N-ヒドロキシ－１－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)ピペラジン－２－カルボキサミド。

前記(製造法１０)の方法に従い、下記化合物を製造することができる。



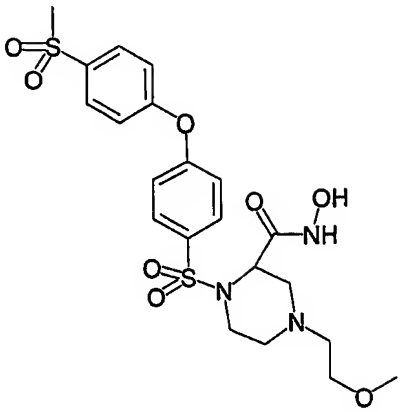
N-ヒドロキシ-１-({４-[４-(メチルスルホニル)フェノキシ]フェニル}スルホニル)ピペラジン-２-カルボキサミド。

前記(製造法９)の方法に従い、下記化合物を製造することができる。



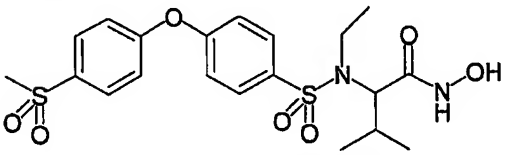
Ｎ－ヒドロキシ－４－({４－[４－(メチルスルホニル)フェノキシ]フェニル}スルホニル)モルホリン－３－カルボキサミド。

前記(製造法１１)の方法に従い、下記化合物を製造することができる。



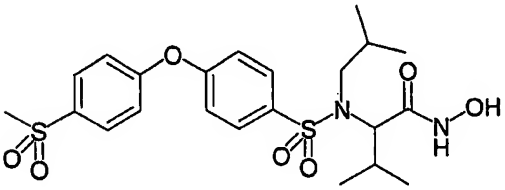
N－ヒドロキシ－４－（２－メトキシエチル）－１－（｛４－［４－（メチルスルホニル）フェノキシ］フェニル｝スルホニル）ピペラジン－２－カルボキサミド。

実施例２と同様にして、下記化合物を製造することができる。



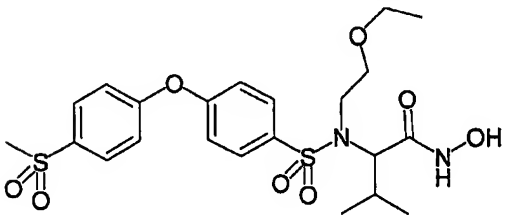
N^2－エチル－N^1－ヒドロキシ－N^2－（｛４－［４－（メチルスルホニル）フェノキシ］フェニル｝スルホニル）バリナミド。

実施例２と同様にして、下記化合物を製造することができる。



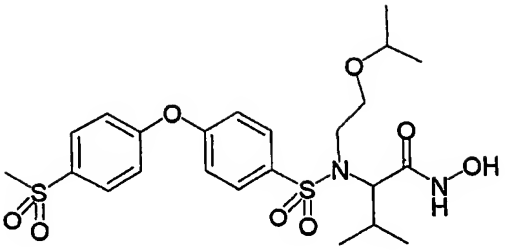
N^1－ヒドロキシ－N^2－イソプチル－N^2－（｛４－［４－（メチルスルホニル）フェノキシ］フェニル｝スルホニル）バリナミド。

実施例４と同様にして、下記化合物を製造することができる。



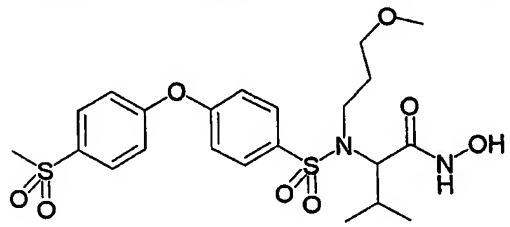
N^1－ヒドロキシ－N^2－（２-エトキシエチル）－N^2－（｛４－［４－（メチルスルホニル）フェノキシ］フェニル｝スルホニル）バリナミド。

実施例４と同様にして、下記化合物を製造することができる。



N^1－ヒドロキシ－N^2－（２－イソプロポキシエチル）－N^2－（{４－[４－（メチルスルホニル）フェノキシ]フェニル}スルホニル）バリナミド。

実施例４と同様にして、下記化合物を製造することができる。



N^1－ヒドロキシ－N^2－（２－メトキシプロピル）－N^2－（{４－[４－（メチルスルホニル）フェノキシ]フェニル}スルホニル）バリナミド。

製剤例１

錠剤の製造

各成分を混合し、必要に応じて造粒した後、打錠することで、錠剤を製造することができる。

組　成	量（ｍｇ／錠剤）
実施例２の化合物	２０
乳糖	７０
トウモロコシデンプン	１７
低置換度ヒドロキシプロピルセルロース	８
ヒドロキシプロピルセルロース	４
ステアリン酸マグネシウム	１
合　　計	１２０

製剤例２

錠剤の製造

各成分を混合し、必要に応じて造粒した後、打錠することで、錠剤を製造する

ことができる。

組　成	量(ｍｇ／錠剤)
実施例２４の化合物	２０
Ｄ－マンニトール	６０
リン酸水素カルシウム	２５
カルメロースカルシウム	8
ヒドロキシプロピルメチルセルロース	4
タルク	3
合　　計	１２０

試験例

ＴＴＣ緩衝液はMMＰ－２酵素アッセイキットに付属しており、組成は５０mM ｔｒｉｓ、１mM塩化カルシウム溶液、０．０５％TritonX－100溶液からｐＨ７．５に調製した溶液である。

ＡＢＴＳはMMＰ－２酵素アッセイキットに付属している。

Streptavidin－ＰＯＤはストレプトアビジン-ペルオキシダーゼを表す。

Ｔｒｉｓ－ＨＣｌは２－アミノ－２－ヒドロキシメチル－１，３－プロパンジオール塩酸塩である。

０．０５％Ｂｒｉｊ３５はポリオキシエチレンドデシルエタンの０．０５％溶液である。

２．５mM ４－アミノフェニル水銀アセテート(AMPA)溶液は、４－アミノフェニル水銀アセテート(35ミリグラム)、０．１規定水酸化ナトリウム水溶液(10ml)、ＴＴＣ緩衝液(30ml)からｐＨ７．０から７．５となるように調製した溶液である。

NaN_3はナトリウムアジドを表わす。

MOCAc-Pro-Leu-Gly-Leu-A2pr(DNP)-Ala-Arg-NH_2は(７-メトキシクマリン-４-イル)-Pro-Leu-Gly-Leu-Ｌ-[N-(２，４-ジニトロフェニル)-Ｌ-２，３-ジアミノプロピオニル]-Ala-Arg-NH_2(ペプチド研)である。

ＤＭＳＯはジメチルスルホキシドを意味する。

ＭＯＰＳは３－(Ｎ－モルホリノ)プロパンスルホン酸を意味する。

試験例１　ＭＭＰ－３阻害活性測定試験

ＭＭＰ－３活性化

ヒトプロストロメリジンｃＤＮＡのＣ末端が切断された物をサブクローニングし(proMMP-3, cDNA sequence in Nature, 348, 699-704 (1990))、大腸菌で発現、更にBiochemistry 30, 6476-6483 (1991)の記載にしたがって精製された。ｐｒｏＭＭＰ－３の活性化は、１mM ４－アミノフェニル水銀アセテートで６０分間３７℃で処理することにより行われた。

阻害試験方法

酵素活性試験をC. G. Knightの方法 (FEBS Lett., 296(3), 263-266 (1992))に従って行った。

活性ＭＭＰ－３(20nM、10μl)、緩衝液(70μl、100mM Tris-HCl溶液、10mM 塩化カルシウム溶液、１００mM塩化ナトリウム溶液および０．０５％Ｂｒｉｊ－３５溶液を含むｐＨ７．５溶液)、MOCAc-Pro-Leu-Gly-Leu-A2pr(DNP)-Ala-Arg-NH_2の０．１％ＤＭＳＯ溶液 (100μM,10μl)と被験化合物のＤＭＳＯ溶液を１．５時間、３７℃でインキュベーションした。混合物を９６孔のプレート上に１００μl／ウェルで処理し、３７℃で培養、化合物存在下での酵素活性を蛍光強度(λex 320nm、λem 405nm)測定し、IC_{50}を算出した。

試験例２　ＭＭＰ－１３阻害活性測定試験

ＭＭＰ－１３活性化

プロコラーゲナーゼ－3(proMMP-13)ｃＤＮＡのＣ末端が切断された物をサブクローニングする(J.Biol.Chem., 269(24), 16766-16773 (1994))ため、２個の合成オリゴヌクレオチドプライマー

(5'-GGAATTCCATATGCTGCCGCTGCCGAGTGGTGGTG ATGAAGATG-3' および

5'-TTTGGATCCTTAGCCGTACAGGCTTTGAATACCTTGTACATCGTCATCAGG-3' :前者は最初のメチオニンを含む特有のNdeI部(下線部)のための配列が組み込まれており、後者は終止コドンとBamHI部(下線部)のための配列を有する。）が、ヒト軟骨細胞ｃＤＮＡライブラリーと共にＰＣＲで用いられた。これらのプライマーとＰｆｕ ＤＮＡ ポリメラーゼ (STRATAGENE)によりＰＣＲで、完全なＭＭＰ－１３の８４の

アミノ酸の原配列と１６４のアミノ酸とをコードする７６７ bp フラグメントが生成した。該フラグメントはNdeIとBamHIとで取出され、pET11a (STRATAGENE)のNdeIおよびBamHI部に接続され、Ｅ．ｃｏｌｉ BL２１(DE3)中に形質転換され培養された。粗製の細胞抽出物がBiochemistryの記載にしたがって調製された。該抽出物を２０ mM Tris－HCl(pH7.2)／５mM ＣａＣｌ$_2$／０．０２％ ＮａＮ$_3$溶液で透析し、ＳＰ－セファロースＨＰカラム(1.6 x 10 cm、アマシャムーファルマシアバイオテック)に処し、溶出を５０ｍｌの０から０．３m塩化ナトリウム溶液の直線的変化により行った。(一部精製したproMMP-13は約0.2Mで溶出した。)溶出分画を２０mM Ｔｒｉｓ－ＨＣｌ(pH7.9)／５mM ＣａＣｌ$_2$／２００mM $(NH_4)_2SO_4$／０．０２％ ＮａＮ$_3$溶液で透析し、フェニルセファロースＨＰカラム(1.6 x 5cm、アマシャムーファルマシアバイオテック)に付し、溶出を０．２Mから０M硫酸アンモニウム溶液の直線的変化により行った。(精製したproMMP-13は約50mMで溶出した。)溶出分画をＹＭ－５限外濾過膜で濃縮、４－アミノフェニル水銀アセテートで活性化し、活性ＭＭＰ－１３をBiochemistry誌の記載に従いゲル濾過クロマトグラフィーによりプロペプチド断片から分離した。

阻害試験方法

酵素活性試験をC. G. Knightの方法(FEBS Lett., 296(3), 263-266 (1992))に従って行った。

活性ＭＭＰ－１３(20nM、10μl)、緩衝液(70μl、100mM Tris-HCl溶液、10mM塩化カルシウム溶液、100mM塩化ナトリウム溶液および0.05%Brij-35溶液を含むpH7.5溶液)、MOCAc-Pro-Leu-Gly-Leu-A2pr(DNP)-Ala-Arg-NH_2の０．１％ＤＭＳＯ溶液(100μM,10μl)と被験化合物のＤＭＳＯ溶液を１．５時間、３７℃でインキュベーションした。混合物を９６ウエルのプレート上に１００μl/ウェルで処理し、３７℃で培養、化合物存在下での酵素活性を蛍光強度(λex 320nm、λem 405nm)測定し、IC_{50}を算出した。

試験例３　ＭＭＰ－２阻害活性測定試験

ＭＭＰ－２酵素アッセイキット(Gelatinase Activity Assay、ロッシュ・ダイアゴニスティックス)を使用した。

MMP－2活性化

1．2UヒトMMP－2(20μl、ベーリンガーマンハイム 30U凍結乾燥品)、TTC緩衝液(980μl)、2．5mM 4－アミノフェニル水銀アセテート溶液(144μl)を37℃で30分間インキュベートした後、使用時まで氷冷下で保存した。

阻害試験方法

所定濃度の化合物のDMSO溶液(2μl)、ビオチン標識されたゼラチン(188μl)、活性化MMP－2の溶液(10μl)を96 ウエルアッセイプレート(タンパク非吸着型)のウェルに入れ、よく振盪し、37℃で1時間インキュベーションした。この溶液をStreptavidinをコーティングしたプレートに移し、15℃から30℃で30分間振盪した。その後、3回TTC緩衝液(200μl)で洗浄した。更にStreptavidin－POD(200μl)を添加し、15℃から25℃ で60分間振盪したのち、3回TTC緩衝液(200μl)で洗浄した。ついで、ABTS 溶液(200μl)を加え、室温で40分放置後、蛍光強度405nmで測定し、IC_{50}を算出した。

尚、上記測定にあたり、コントロールおよびブランクはウェル調製時に以下のように調製した。コントロールはサンプル溶液の替りにDMSO(2μl)を加えた。また、ブランクはサンプル溶液の替りにDMSO(2μl)を加え、かつ活性化MMP－2溶液(10μl)の替りに、1．2UヒトMMP－2を加えずに活性化MMP－2溶液調製時と同様に調製した溶液(10μl)を加えた。

試験例4 MMP－9阻害活性測定試験

MMP－9活性化

緩衝液(190μl；50mM Tris-HCl溶液、0.5m塩化ナトリウム溶液、5mM塩化カルシウム溶液、からpH7.5に調整したもの)、ヒトMMP－9(10μl)、トリプシン溶液(20μl；トリプシン3mg を5 ml 活性化緩衝液に溶解)を混合し、37℃で10分間インキュベーションした。これにアプロチニン 溶液(20μl；アプロチニン3mgを5ml緩衝液に溶解)を加え、37℃で10分間インキュベーションした。ついで、緩衝液 (2ml)を追加した。これを使用時まで氷冷下で保存した。

阻害試験方法

所定濃度の化合物のＤＭＳＯ溶液(2μl)、ビオチン標識されたゼラチン(188μl)、活性化ＭＭＰ－９の溶液(10μl)を９６ウエルアッセイプレート(タンパク非吸着型)のウェルに入れ、よく振盪し、３７℃で１時間インキュベーションした。この溶液をストレプトアビジンをコーティングしたプレートに移し、１５℃から３０℃で３０分間振盪した。その後、３回ＴＴＣ緩衝液(200μl)で洗浄した。更にStreptavidin－ＰＯＤ(200μl)を添加し、１５℃から２５℃で６０分間振盪したのち、３回ＴＴＣ緩衝液(200μl)で洗浄した。ついで、ＡＢＴＳ溶液(200μl)を加え、室温で４０分放置後、蛍光強度４０５ｎｍで測定し、IC_{50}を算出した。

なお、上記測定にあたり、コントロールはサンプル溶液の替りにＤＭＳＯ(2μl)を加えた。また、ブランクはサンプル溶液の替りにＤＭＳＯ(2μl)を加え、かつ活性化ＭＭＰ－９溶液(10μl)の替りに、１．２ＵヒトＭＭＰ－９を加えずに活性化ＭＭＰ－２溶液調製時と同様に調製した溶液(10μl)を加えた。

試験例５　ＭＭＰ-１４(ＭＴ１-ＭＭＰ)阻害活性測定試験

ヒトリコンビナントＭＴ1－ＭＭＰはメーカー；バイオジェネシス社、購入先；コスモバイオ(ナカライテスク)を使用した。

阻害試験方法

アッセイ緩衝液(70μl;0.1M Tris-HCl溶液，0.1M 塩化ナトリウム溶液，10mM 塩化カルシウム溶液，0.05% Brij35からpH7.5に調製した溶液)、化合物の0.1% w/wDMSO溶液(10μl)、ＭＭＰ基質溶液(10μl; MOCAc-Pro-Leu-Gly-Leu-A2pr(DNP)-Ala-Arg-NH_2、ペプチド研をアッセイ緩衝溶液で50μMに希釈した溶液)、ヒトリコンビナントＭＴ１－ＭＭＰ(0.4pg/10μl/ウェル)をよく撹拌振盪した。これを蛍光プレートリーダーにて測定した(λex320nm/λem405nm)。３７℃で０．５時間インキュベーションした後、各時間ごとに蛍光プレートリーダーにて測定し(λex320nm/λem405nm)、IC_{50}を算出した。

阻害値はＭＴ１－ ＭＭＰを添加したウェルの蛍光平均値から、ブランクのウェルの平均値を差し引いた値から算出した。なお、ブランクとしては、ＭＴ１－ ＭＭＰ溶液の代わりにAssay bufferを１０μl添加した混合液を用いた。

試験例６　ＭＭＰ－１阻害活性測定試験

ＭＭＰ-1 （間質コラゲナーゼ：EC3.4.24.7、ヒトリューマチ滑膜線維芽細胞、calbiochem cat.444208)は３７℃で６０分間ＡＭＰＡで活性化した。被験物質は５０mM ＭＯＰＳ(pH7.2)、１０mM塩化カルシウム水溶液、１０μM塩化亜鉛を含んだ反応混合物中、活性化ＭＭＰ－１と３７℃で６０分間プレインキュベートした。これに２５μMMca-Pro-Leu-Dpa-Ala-Arg-NH_2を加えて、３７℃で１２０分間インキュベートした。酵素活性はMca-Pro-Leu-Glyの蛍光強度により測定し、ＩＣ$_{50}$を算出した。

試験例１～６の結果を表３に示した。尚、表中の阻害活性値はＩＣ$_{50}$値(nM)を表す。

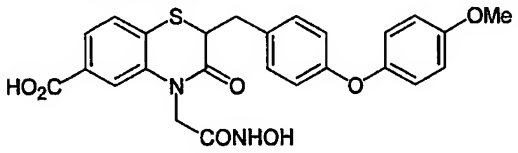
表３

ＭＭＰ活性

実施例	MMP－13 阻害活性値	MMP-3 阻害活性値	MMP-14 阻害活性値	MMP-2 阻害活性値	MMP-9 阻害活性値	MMP-1 阻害活性値
比較例1	7.4	88	87.3	>100	>100	NT
実施例2	5.7	21.2	3802	<100	300	7210
実施例3	0.5	4.8	172	>100	1000	NT
実施例5	1.3	15.4	105	100	>100	NT
実施例10	34.4	85.8	>5000	2400	6800	NT
実施例12	4	16	893.3	<100	<100	>10000
実施例13	10.8	13.5	>5000	900	4700	>10000
実施例15	24.6	5.2	>5000	300	700	NT
実施例18	3.1	29.9	799	100	500	3300
実施例22	1.9	26.6	668	1200	1400	>10000
実施例23	4.1	21.6	>5000	2100	2300	>10000
実施例24	16.3	128.2	>5000	>10000	>10000	NT
実施例26	1.9	14.3	395.4	300	>100	3900
実施例27	21.3	89.4	>5000	>10000	>10000	NT
実施例31	11.2	59	>5000	800	4900	NT
実施例36	3.81	37.1	937.8	2900	>100	NT
実施例42	4.02	67.5	>5000	<100	4300	>10000
実施例43	<0.5	8.5	82	1500	600	NT
実施例44	0.5	2.7	343	>100	>10000	NT
実施例45	0.6	1.5	>1500	>100	>100	4960
実施例46	10.5	11.6	>1500	>100	>100	NT
実施例48	6.9	35.9	>1500	>100	>100	NT
実施例50	3	38	>1000	>100	244	NT

ＮＴ：未試験

なお、比較例１の化合物は下記式で示され、上記実施例４９および５０と同様にして製造した。



試験例７　アジュバント関節炎(インビボ)

実験動物としてLewis系雄性ラットを用いた。Mycobacterium butyricumの死菌菌体を０．５％の濃度になるように流動パラフィンに懸濁した液をラットの右側後肢足蹠皮下に注入した。１０日後に左側後肢にも明確な２次炎症の発症の見られた動物を選び、０．５％メチルセルロース溶液に懸濁させた本発明化合物(実施例２の化合物)を１２日間連続1日１回経口投与し、投与終了から５時間後の後肢容積を投与開始時の後肢容積と比較し、この差により腫脹抑制作用の評価を行った。

その結果を表４に示した。

表４

投与化合物	経口投与量 (mg/kg)	動物数(匹)	浮腫量の増加(ml)	
			注射足	非注射足
コントロール	-	10	-0.24±0.45	1.07±0.31
実施例２	50	10	-1.06±0.47**	0.74±0.16**

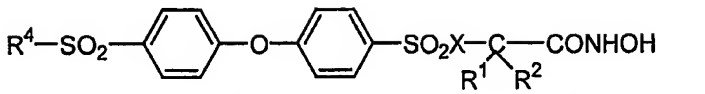
**: P<0.01(t 検定)

試験例８　ラット半月板切除モデル試験(インビボ)

実験動物として６週齢のSD(IGS)系雄性ラットを用いた。右後肢の関節の半月板を部分的に切除した。実施例２の化合物を１日１回５０mg/kgを３週間経口投与した。関節部の組織標本を作製し、サフラニンO/ファーストグリーン染色を施し、軟骨変性を評価した。病態コントロール群の軟骨変性の程度を１００％とし、被験薬投与群の軟骨の変性程度を算出した。軟骨変性率は３３％であった。(*；$p < 0.05$, Steel-test)

請 求 の 範 囲

1． 一般式(1)



[式中、R^1およびR^2は、互いに独立して水素原子、置換もしくは無置換の低級アルキル基、または低級ハロアルキル基を表わすか、あるいはR^1およびR^2は互いに結合して、炭素数２～７の直鎖アルキレン基を表わすか、または式－(CH_2)m－Y－(CH_2)q－で表わされる基を表わし(ただし、Yは－O－、－NR^5－、－S－、－SO－、または－SO_2－を表わし、mおよびqは、互いに独立して１～５の整数を表わし、かつ、mとqとの和が２～６であり、そしてR^5は、水素原子、置換もしくは無置換の低級アルキル基、置換もしくは無置換の低級アルキルカルボニル基、置換もしくは無置換の低級アルコキシカルボニル基、置換もしくは無置換の低級アルキルスルホニル基、置換もしくは無置換のスルファモイル基、または置換もしくは無置換のカルバモイル基を表わす。)、Xは、メチレン基またはNR^3を表わし(ただし、R^3は水素原子、または置換もしくは無置換の低級アルキル基を表わすか、あるいはR^3はR^1と一緒になって、それらが結合するN原子および炭素原子と共に、置換もしくは無置換のヘテロシクロアルカンを形成してもよい。)、そしてR^4は、炭素数１～４の低級アルキル基を表わす。]

で表されるヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

2． 一般式(1)において、R^1およびR^2が、互いに独立して水素原子、または炭素数１～３の低級アルキル基である請求項１記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

3． 一般式(1)において、R^1およびR^2が互いに結合した炭素数３～５のアルキレン基である請求項１記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

4． 一般式(1)において、R^1およびR^2が、互いに結合して式－(CH_2)m－Y－(CH_2)q－で表わされる基である請求項１記載のヒドロキサム酸誘導体、そ

の薬学的に許容される塩、またはそのプロドラッグ。

5． 一般式(1)の式－(CH_2)m－Y－(CH_2)q－において、mとqが共に2である請求項4記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

6． 一般式(1)において、XがN－R^3であり、該R^3が、水素原子、炭素数1～4の低級アルキル基、または、カルボキシ基、フェニル基(該フェニル基は低級アルキル基、低級アルコキシ基またはハロゲン原子で置換されていてもよい。)、2－ピリジル基、3－ピリジル基、4－ピリジル基、フリル基、チエニル基(該ピリジル基、フリル基およびチエニル基は低級アルキル基で置換されていてもよい。)、低級アルコキシカルボニル基、低級アルコキシ基、もしくは低級シクロアルコキシ基で置換された炭素数1～4の低級アルキル基である請求項1記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

7． 一般式(1)において、XがN－R^3であり、該R^3が、R^1と一緒になって、それらが結合するN原子および炭素原子と共に、それぞれ置換もしくは無置換のピロリジン、ピペリジン、ピペラジン、モルホリンまたはチオモルホリンを形成する請求項1記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

8． 一般式(1)において、Xがメチレン基であり、R^1およびR^2が、互いに結合した炭素数3～4の直鎖アルキレン基、または－(CH_2)$_2$－O－(CH_2)$_2$－である請求項1記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

9． 一般式(1)において、R^4がメチル基である請求項1～8のいずれかに記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

10． 一般式(1)において、R^1およびR^2が、互いに独立して水素原子または炭素数1～4の低級アルキル基であるか、あるいはR^1およびR^2が、互いに結合した炭素数3～4の直鎖アルキレン基、または式－(CH_2)$_2$－Y－(CH_2)$_2$－であり、XがN－R^3であり、該R^3が水素原子、炭素数1～4の低級アルキル基、

または、カルボキシ基、フェニル基(該フェニル基は低級アルキル基、低級アルコキシ基またはハロゲン原子で置換されていてもよい。)、２－ピリジル基、３－ピリジル基、４－ピリジル基、フリル基、チエニル基(該ピリジル基、フリル基およびチエニル基は低級アルキル基で置換されていてもよい。)、低級アルコキシカルボニル基、低級アルコキシ基もしくはシクロアルコキシ基で置換された炭素数１～４の低級アルキル基であり、そしてR^4がメチル基である請求項１記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

１１．　一般式(１)において、R^1およびR^2が互いに結合した炭素数３～４の直鎖アルキレン基、または－$(CH_2)_2$－O－$(CH_2)_2$－であり、XがN－R^3であり、そのR^3が炭素数１～４の低級アルコキシ基で置換されていてもよい炭素数１～４の低級アルキル基である請求項１記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグ。

１２．　請求項１～１１のいずれかに記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグを有効成分として含有するMMP－３および／またはMMP－１３選択的阻害剤であることを特徴とするMMP阻害剤。

１３．　MMP－１およびMMP－１４に対して非選択的であることを特徴とする請求項１２記載のMMP阻害剤。

１４．　MMP－２およびMMP－９に対して非選択的であることを特徴とする請求項１３記載のMMP阻害剤。

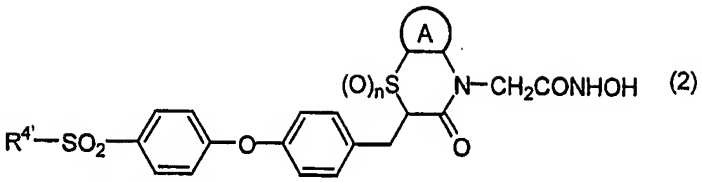
１５．　請求項１～１１のいずれかに記載のヒドロキサム酸誘導体、その薬学的に許容される塩、またはそのプロドラッグを有効成分として含有するMMP－３および／またはMMP－１３の機能亢進が関与する疾患の治療または予防剤。

１６．　MMP－３および／またはMMP－１３の機能亢進が関与する疾患が、関節炎である請求項１５記載の治療または予防剤。

１７．　関節炎が、変形性関節症または慢性関節リウマチである請求項１６記載の治療剤または予防剤。

１８．　MMP－３、および／またはMMP－１３の機能亢進が関与する疾患が、炎症性疾患である請求項１５記載の治療または予防剤。

１９．　一般式(２)



[式中、環Ａは置換もしくは無置換のベンゼン環または芳香族５～６員ヘテロ環を表わし、Ｒ４’は炭素数１～４の低級アルキル基を表わし、そしてｎは０～２の整数を意味する。]

で表わされる化合物を有効成分とするＭＭＰ－１およびＭＭＰ－１４に対して非選択的であることを特徴とするＭＭＰ－３および／またはＭＭＰ－１３阻害剤。

SEQUENCE LISTING

<110> SUMITOMO PHARMACEUTICALS COMPANY, LIMITED

<120> Hydroxamic acid derivative and MMP Inhibitor containing said derivative as active ingredient

<130> 663577

<150> JP 2001-397638

<151> 2001-12-27

<160> 3

<210> 1

<211> 44

<212> DNA

<213> Artificial Sequence

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<212> DNA

<213> Artificial Sequence

<400> 2

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<210> 3

<211> 6

<212> PRT

<213> Artificial Sequence

<223> Xaa at position 1 means 7-methoxycoumalin-4-yl proline and Xaa at position 5 means L-[N-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl]-alanine.

<400> 3

Xaa Leu Gly Leu Xaa Arg

1 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/13580

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C317/22, C07D213/42, C07D279/16, C07D295/18, C07D309/14, C07D309/08, A61K31/10, A61K31/18, A61K31/351, A61K31/4406, A61K31/4409, A61K31/5375, A61K31/5415, A61P19/02, A61P29/00,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C317/22, C07D213/42, C07D279/16, C07D295/18, C07D309/14, C07D309/08, A61K31/10, A61K31/18, A61K31/351, A61K31/4406, A61K31/4409, A61K31/5375, A61K31/5415, A61P19/02, A61P29/00,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/71514 A1 (G.D. SEARLE & CO.), 30 November, 2000 (30.11.00), & JP 2003-500389 A & EP 1178959 A1	1-18
A	WO 00/63197 A1 (Sumitomo Pharmaceuticals Co., Ltd.), 26 October, 2000 (26.10.00), & JP 2002-542238 A & EP 1173427 A1	19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 April, 2003 (07.04.03)	30 April, 2003 (30.04.03)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/13580

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The subject matters of the claims are classified into the following groups.

1 Claims 1-18

A compound represented by the general formula (1) and a medicinal use of the same.

2 Claim 19

A medicinal use of a compound represented by the general formula (2).

Between these groups, there is no relationship involving any special technical feature common to these. Consequently, these groups are not considered to be so linked as to form a single general inventive concept.

(continued to extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/13580

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl[7] A61P43/00

(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED
Minimum Documentation Searched(International Patent Classification (IPC))

Int.Cl[7] A61P43/00

Minimum documentation searched (classification system followed by classification symbols)

Continuation of Box No.II of continuation of first sheet(1)

Therefore, the number of inventions disclosed in the claims of this international application is 2.

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ０２／１３５８０

A.　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl.⁷　C07C317/22, C07D213/42, C07D279/16, C07D295/18, C07D309/14, C07D309/08, A61K31/10, A61K31/18, A61K31/351, A61K31/4406, A61K31/4409, A61K31/5375, A61K31/5415, A61P19/02, A61P29/00, A61P43/00

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl.⁷　C07C317/22, C07D213/42, C07D279/16, C07D295/18, C07D309/14, C07D309/08, A61K31/10, A61K31/18, A61K31/351, A61K31/4406, A61K31/4409, A61K31/5375, A61K31/5415, A61P19/02, A61P29/00, A61P43/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS(STN), REGISTRY(STN)

C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	WO 00/71514 A1(G.D. SEARLE & CO.) 2000.11.30 & JP 2003-500389 A & EP 1178959 A1	1～18
A	WO 00/63197 A1(SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 2000.10.26 & JP 2002-542238 A & EP 1173427 A1	19

☐ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
０７．０４．０３	30.04.03

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）		
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	本堂裕司 印	4H	9049
	電話番号　０３－３５８１－１１０１　内線　３４４３		

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９８年７月）

国際調査報告

国際出願番号　PCT／JP02／13580

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．☐ 請求の範囲 _____ は、この国際調査機関が調査をすることを要しない対象に係るものである。
つまり、

2．☐ 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3．☐ 請求の範囲 _____ は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅱ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

請求の範囲に記載された発明はそれぞれ、
①請求の範囲１～１８
一般式（１）で表される化合物およびその医薬用途
②請求の範囲１９
一般式（２）で表される化合物の医薬用途
の群に区分され、それぞれの群の間は共通する特別な技術的特徴を含む関係にないから、単一の一般的発明概念を形成するように連関しているものとは認められない。
したがって、請求の範囲に記載されている国際出願の発明の数は２である。

1．☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．☒ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．☐ 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意
☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014389 A1

(51) International Patent Classification[7]: A61K 31/5415, C07D 265/36, 279/16, 417/14, 413/12, 417/06, 215/22, 401/12, 498/04, 513/04, 471/04, 405/06, A61P 29/00, A61K 31/4375, 31/4704, 31/4709, 31/538, 31/5383, 31/542

(21) International Application Number:
PCT/IB2003/003537

(22) International Filing Date: 4 August 2003 (04.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/403,082 13 August 2002 (13.08.2002) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY LLC [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: O'BRIEN, Patrick, Michael [US/US]; Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: LUMB, Trevor, J. et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

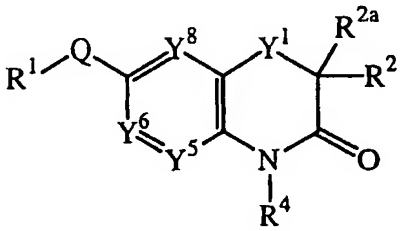
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 3,4-DIHYDROQUINOLIN-2-ONE, 5,6-FUSED OXAZIN-3-ONE, AND 5,6-FUSED THIAZIN-3-ONE DERIVATIVES AS MATRIX METALLOPROTEINASE INHIBITORS



(I)

(57) Abstract: This invention provides compounds defined by Formula I or a pharmaceutically acceptable salt thereof, wherein R^1, Q, Y^1, Y^5, Y^6, Y^8, R^2, R^{2a}, and R^4 are as defined in the specification. The invention also provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, as defined in the specification, together with a pharmaceutically acceptable carrier, diluent, or excipient. The invention also provides methods of inhibiting an NTW-13 enzyme in an animal, comprising administering to the animal a compound of Formula I, or a pharmaceutically acceptable salt thereof. The invention also provides methods of treating a disease mediated by an MMI'-13 enzyme in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition. The invention also provides methods of treating diseases such as heart disease, multiple sclerosis, osteo- and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, cardiac insufficiency, inflammatory bowel disease, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition. The invention also provides combinations, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with another pharmaceutically active component as described in the specification.

WO 2004/014389 A1

3,4-DIHYDROQUINOLIN-2-ONE, 5,6-FUSED OXAZIN-3-ONE, AND 5,6-FUSED THIAZIN-3-ONE DERIVATIVES AS MATRIX METALLOPROTEINASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to 3,4-dihydroquinolin-2-one, 5,6-fused oxazin-3-one, and 5,6-fused thiazin-3-one derivatives which inhibit matrix metalloproteinase enzymes and thus are useful for treating diseases resulting from MMP-mediated tissue breakdown such as heart disease, cardiac insufficiency, inflammatory bowel disease, multiple sclerosis, osteo- and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis.

BACKGROUND OF THE INVENTION

Matrix metalloproteinases (sometimes referred to as MMPs) are naturally occurring enzymes found in most mammals. Over-expression and activation of MMPs, or an imbalance between MMPs and inhibitors of MMPs, have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues.

Stromelysin-1 and gelatinase A are members of the MMP family. Other members include fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), gelatinase B (92 kDa gelatinase) (MMP-9), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11), matrilysin (MMP-7), collagenase 3 (MMP-13), TNF-alpha converting enzyme (TACE), and other newly discovered membrane-associated matrix metalloproteinases (Sato H., Takino T., Okada Y., Cao J., Shinagawa A., Yamamoto E., and Seiki M., *Nature*, 1994;370:61-65). These enzymes have been implicated with a number of diseases which result from breakdown of connective tissue, including such diseases as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal

epidermal and gastric ulceration, atherosclerosis, neointimal proliferation which leads to restenosis and ischemic heart failure, and tumor metastasis. A method for preventing and treating these and other diseases is now recognized to be by inhibiting matrix metalloproteinase enzymes, thereby curtailing and/or eliminating the breakdown of connective tissues that results in the disease states.

There is a catalytic zinc domain in matrix metalloproteinases that is typically the focal point for inhibitor design. The modification of substrates by introducing zinc-chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and the natural endogenous inhibitors of MMPs (TIMPs) have been used successfully to treat animal models of cancer and inflammation. MMP inhibitors have also been used to prevent and treat congestive heart failure and other cardiovascular diseases, United States Patent No. 5,948,780.

A major limitation on the use of currently known MMP inhibitors is their lack of specificity for any particular enzyme. Recent data has established that specific MMP enzymes are associated with some diseases, with no effect on others. The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave native interstitial collagens, and thus are associated only with diseases linked to such interstitial collagen tissue. This is evidenced by the recent discovery that MMP-13 alone is over expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., *J. Am. Chem. Soc.*, 2000;122:9648-9654).

Selective inhibitors of MMP-13 include WAY-170523, which has been reported by Chen et al., supra., 2000, and compounds reported in PCT International Patent Application Publication numbers WO 01/63244; WO 00/09485; WO 01/12611; WO 02/34726; and WO 02/34753, and European Patent Application numbers EP 935,963 and EP 1,138,680. Further, U.S. Patent Number 6,008,243 discloses inhibitors of MMP-13. No selective or nonselective inhibitor of MMP-13 has been approved and marketed for the treatment of any disease in any mammal. The need continues to find new low molecular weight compounds that are potent and selective MMP inhibitors, and that have an acceptable therapeutic index of toxicity/potency to make them amenable for use clinically in

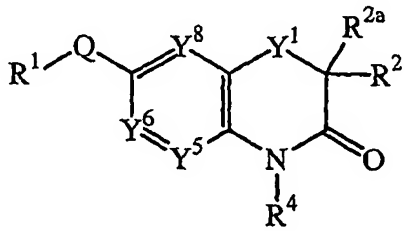
the prevention and treatment of the associated disease states. An object of this invention is to provide a group of selective MMP-13 inhibitor compounds characterized as being 3,4-dihydroquinolin-2-one, 5,6-fused oxazin-3-one, and 5,6-fused thiazin-3-one derivatives.

SUMMARY OF THE INVENTION

This invention provides a 3,4-dihydroquinolin-2-one, 5,6-fused oxazin-3-one, and 5,6-fused thiazin-3-one derived compounds defined by Formula I.

Accordingly, embodiments of the invention include:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C{=}C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-(G)$_m$;

Substituted 3- to 6-membered heterocycloalkyl-(G)$_m$;

5- or 6-membered heteroaryl-(G)$_m$;

Substituted 5- or 6-membered heteroaryl-(G)$_m$;

(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

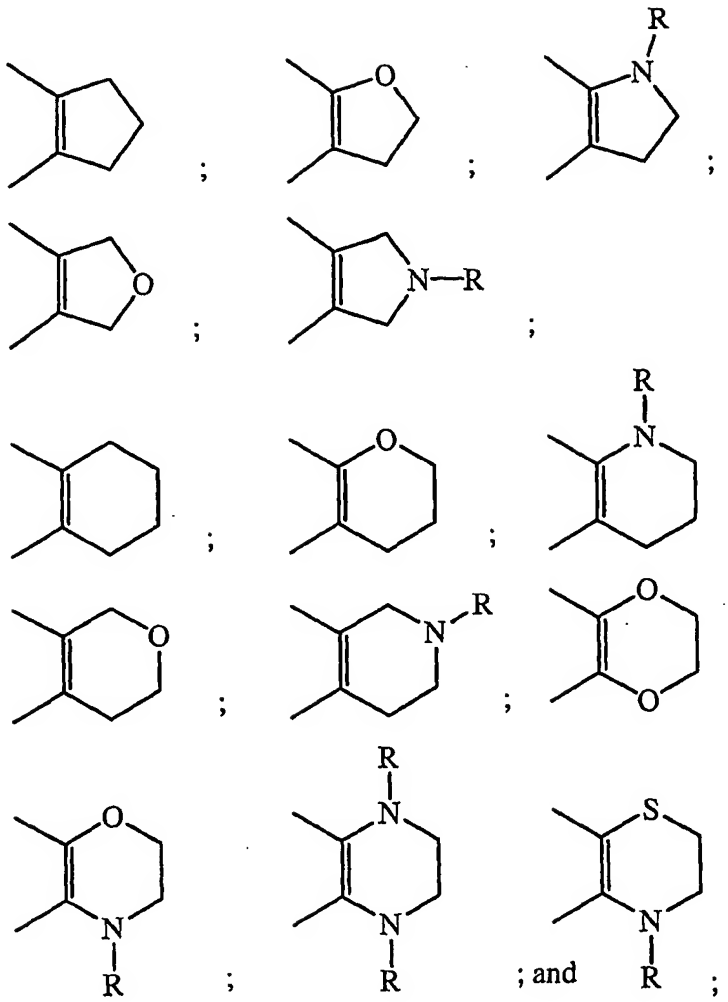
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^1 is O, S, S(O), $S(O)_2$, or CH_2;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

Q is selected from:

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(S)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

SC(O);

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

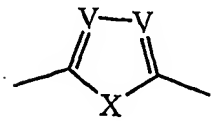
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CCH_2$;

$CF_2C{\equiv}C$; and

$C{\equiv}CCF_2$;



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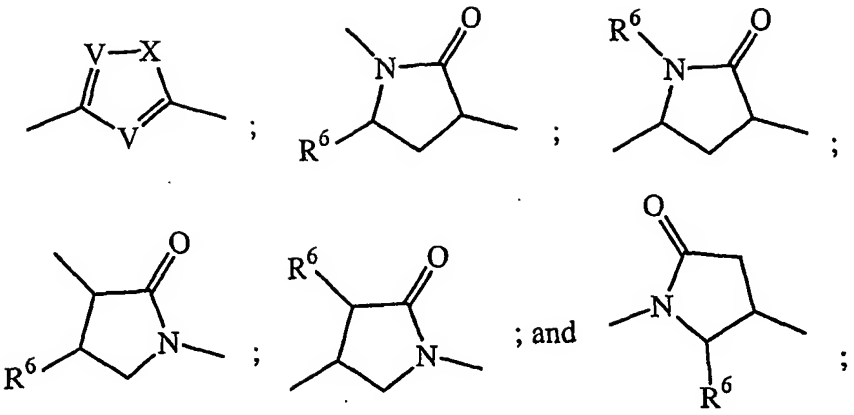


Each R^6 independently is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V is independently C(H) or N;

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6

alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

2. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^5, Y^6, and Y^8 are each C(R^5), wherein each R^5 is independently defined as above.

3. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^5, Y^6, and Y^8 are each C(H).

4. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein at least one of Y^5, Y^6, and Y^8 is N.

5. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^5 is N and Y^6 and Y^8 are each CH.

6. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^6 is N and Y^5 and Y^8 are each CH.

7. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^8 is N and Y^5 and Y^6 are each CH.

8. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein at least two of Y^5, Y^6, and Y^8 are N.

9. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 is O.

10. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 is S.

11. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CH_2.

12. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 is S(O).

13. The compound according to Embodiment 1, or a pharmaceutically acceptable salt thereof, wherein Y^1 is $S(O)_2$

14. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is OC(O).

15. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $CH(R^6)C(O)$.

16. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $OC(NR^6)$.

17. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $CH(R^6)C(NR^6)$.

18. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)C(O)$.

19. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)C(NR^6)$.

20. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $N(R^6)CH_2$.

21. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is SC(O).

22. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $CH(R^6)C(S)$.

23. The compound according to any one of Embodiments 1 to13, or a pharmaceutically acceptable salt thereof, wherein Q is $SC(NR^6)$.

24. The compound according to any one of Embodiments 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Q is $C\equiv C$, $CH_2C\equiv C$, $C\equiv CCH_2$, $CF_2C\equiv C$, or $C\equiv CCF_2$.

25. The compound according to any one of Embodiments 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R^4 is H or CH_3.

26. The compound according to any one of Embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein at least one of R^1 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); or

at least one of R^2 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl)$_m$;

Substituted phenyl-(C_1-C_8 alkylenyl)$_m$;

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$; and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$;

wherein m is an integer of 0 or 1; and

wherein each group and each substituent is independently selected.

27. The compound according to any one of Embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl); and

R^2 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl)$_m$;

Substituted phenyl-(C_1-C_8 alkylenyl)$_m$;

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$; and

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)$_m$;

wherein m is an integer of 0 or 1; and

wherein each group and each substituent is independently selected.

28. The compound according to any one of Embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl); and

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

and R^2 is independently selected from:

Phenyl-(C_1-C_8 alkylenyl)$_m$;

Substituted phenyl-(C_1-C_8 alkylenyl)$_m$;

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$; and

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)$_m$;

wherein m is an integer of 0 or 1; and

wherein each group and each substituent is independently selected.

29. The compound according to any one of Embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl);

3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl); and

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl) and

wherein each group and each substituent recited above is independently selected.

30. The compound according to any one of Embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R^1 is substituted phenyl-(C_1-C_8 alkylenyl).

31. The compound according to any one of Embodiments 1 to 30, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H or CH_3.

32. The compound according to any one of Embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_8 alkylenyl is CH_2, $C(CH_3)_2$, C(=O), or CF_2.

33. The compound according to any one of Embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, wherein each C_1-C_8 alkylenyl is CH_2.

34. The compound according to any one of Embodiments 1 to 33, or a pharmaceutically acceptable salt thereof, wherein at least one substituent is selected from the groups:

CO_2H;

CO_2CH_3;

F;

Cl;

CN;

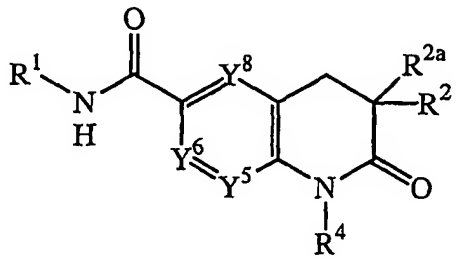
CF_3;

HO;

CH_3O; and

CH_3.

35. A compound of Formula II



II

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group C=C(H)R^2, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-S(O)$_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)S(O)$_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-NS(O)$_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-(G)$_m$;

Substituted 3- to 6-membered heterocycloalkyl-(G)$_m$;

5- or 6-membered heteroaryl-(G)$_m$;

Substituted 5- or 6-membered heteroaryl-(G)$_m$;

(C_1-C_6 alkyl)-S(O)$_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-S(O)$_2$-(C_1-C_8 alkylenyl)$_m$;

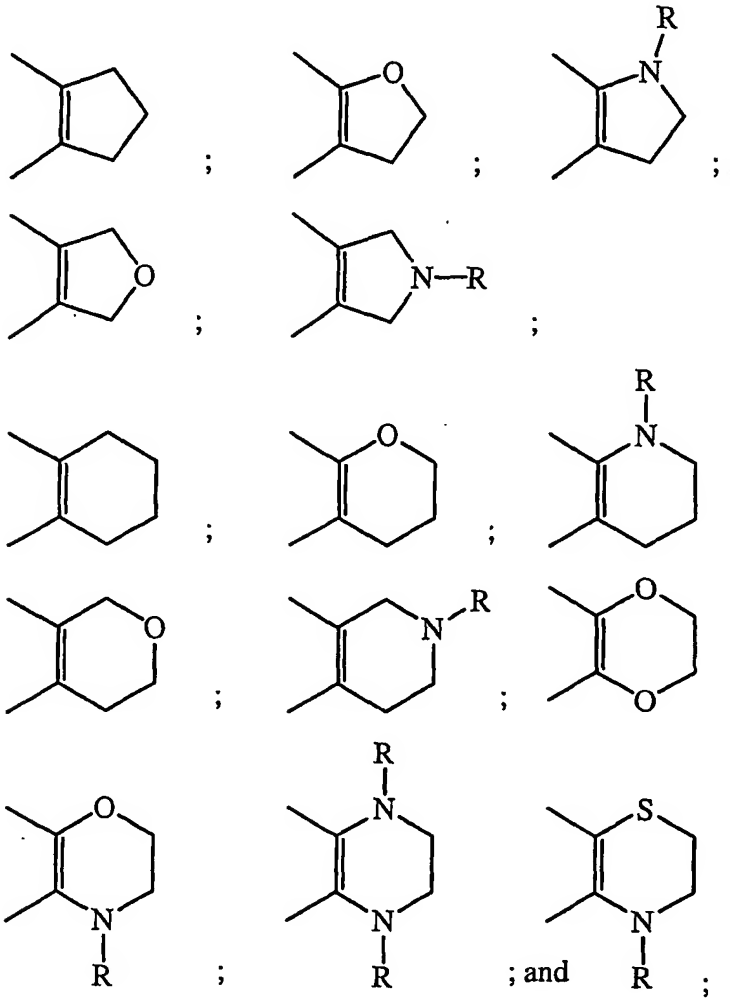
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

36. The compound according to Embodiment 35, selected from:

3-Benzylidene-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 4-methylsulfanyl-benzylamide;

3-(3,5-Difluoro-4-hydroxy-benzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (pyrimidin-5-ylmethyl)-amide; and

3-Biphenyl-4-ylmethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 3-fluoro-benzyl amide;

or a pharmaceutically acceptable salt thereof.

37. The compound according to Embodiment 35, selected from:

5-Methyl-7-(4-methylsulfanyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid (thiazol-2-ylmethyl)-amide;

7-(3-Chloro-benzylidene)-5-methyl-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid benzylamide;

3-(3-Hydroxy-benzylidene)-1-methyl-2-oxo-1,2,3,4-tetrahydro-[1,7]naphthridine-6-carboxylic acid (pyridin-4-ylmethyl)-amide;

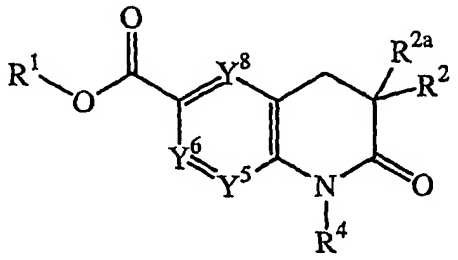
4-(1-Methyl-2-oxo-6-[(pyridin-3-ylmethyl)-carbamoyl]-1,2,3,4-tetrahydro-[1,7]naphthyridin-3-ylmethyl)-benzoic acid;

6-(4-Methanesufanyl-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridine-3-carboxylic acid-4-cyano-benzylamide; and

6-(3-Bromo-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-carboxylic acid 4-fluoro-benzylamide;

or a pharmaceutically acceptable salt thereof.

38. A compound of Formula III



III

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C=C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

$(C_1$-C_6 alkyl)-O;

$(C_1$-C_6 alkyl)-$S(O)_2$;

H_2N;

$(C_1$-C_6 alkyl)-N(H);

$(C_1$-C_6 alkyl)$_2$-N;

$(C_1$-C_6 alkyl)-C(O)O-$(C_1$-C_8 alkylenyl)$_m$;

$(C_1$-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1$-C_6 alkyl)-C(O)N(H)-$(C_1$-C_8 alkylenyl)$_m$;

$(C_1$-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1$-C_8 alkylenyl);

$(C_1$-C_6 alkyl)-N(H)$S(O)_2$-$(C_1$-C_8 alkylenyl)$_m$;

$(C_1$-C_6 alkyl)$_2$-$NS(O)_2$-$(C_1$-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$; $(C_1$-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1$-C_8 alkylenyl)$_m$; and

$(C_1$-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1$-C_8 alkylenyl)$_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

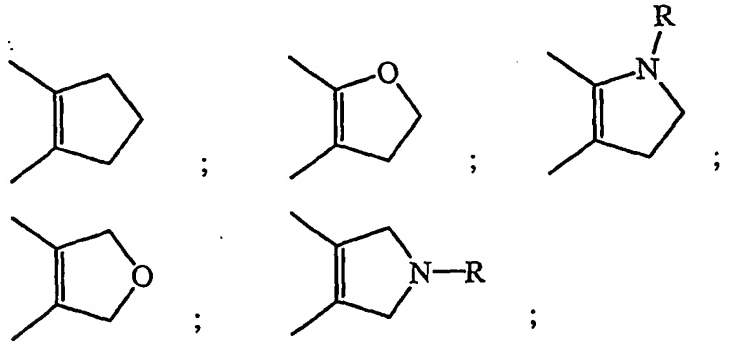
wherein each substituent on a carbon atom may further be independently selected from:

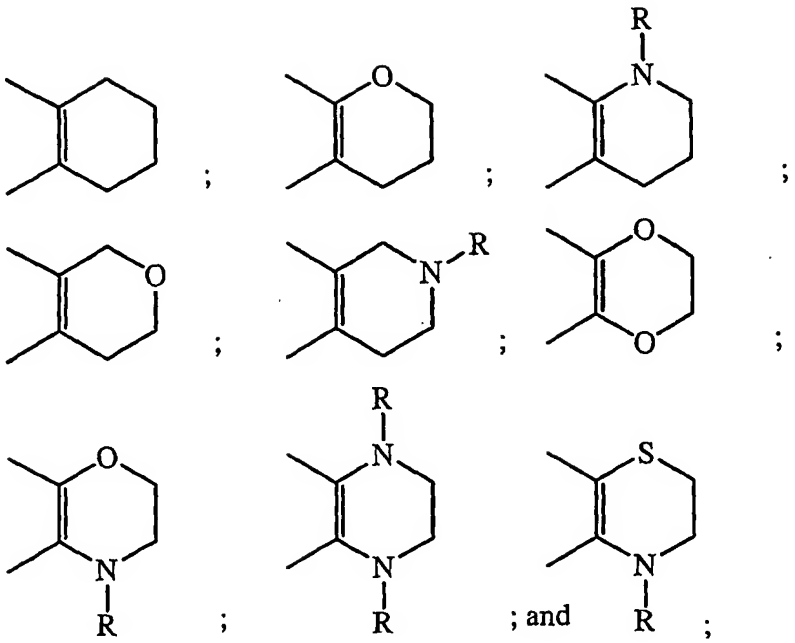
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any $(C_1\text{-}C_6$ alkyl$)_2$-N group, the $C_1\text{-}C_6$ alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

39. The compound according to Embodiment 38, selected from:

3-Benzylidene-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 4-methylsulfanyl-benzyl ester;

3-(3,5-Difluoro-4-hydroxy-benzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (pyrimidin-5-ylmethyl)-ester; and

3-Biphenyl-4-ylmethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 3-fluoro-benzyl ester;

or a pharmaceutically acceptable salt thereof.

40. The compound according to Embodiment 38, selected from:

5-Methyl-7-(4-methylsulfanyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid (thiazol-2-ylmethyl)-ester;

7-(3-Chloro-benzylidene)-5-methyl-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid benzyl ester;

3-(3-Hydroxy-benzylidene)-1-methyl-2-oxo-1,2,3,4-tetrahydro-[1,7]naphthridine-6-carboxylic acid (pyridin-4-ylmethyl)-ester;

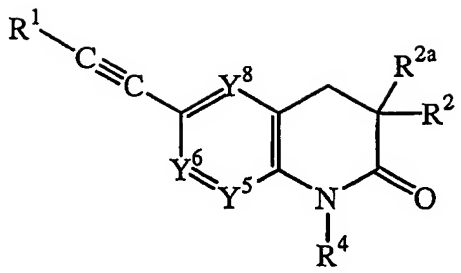
4-(1-Methyl-2-oxo-6-[(pyridin-3-ylmethyl)-oxycarbonyl]-1,2,3,4-tetrahydro-[1,7]naphthyridin-3-ylmethyl)-benzoic acid;

6-(4-Methanesufanyl-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridine-3-carboxylic acid-4-cyano-benzyl-ester; and

6-(3-Bromo-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-carboxylic acid 4-fluoro-benzyl-ester;

or a pharmaceutically acceptable salt thereof.

41. A compound of Formula IV



IV

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C=C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

$(C_1\text{-}C_6$ alkyl)-C(O)O-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl);

$(C_1\text{-}C_6$ alkyl)-N(H)$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)$_2$-$NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl)$_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

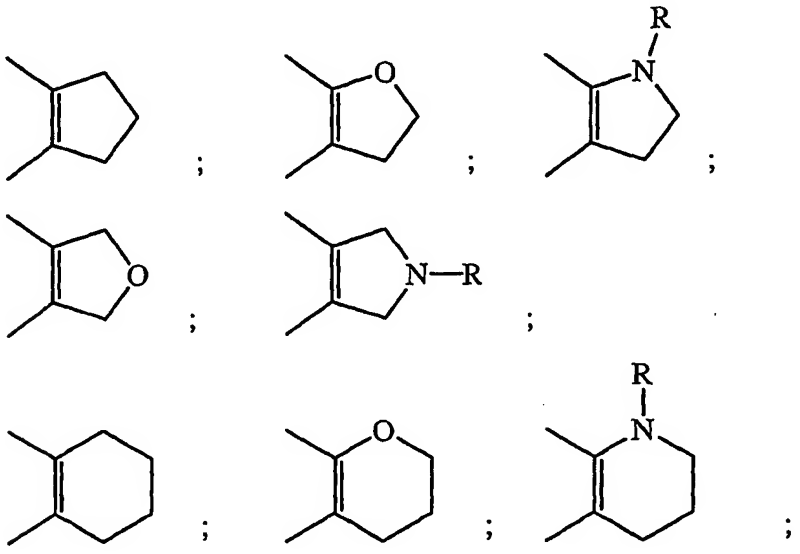
wherein each substituent on a carbon atom may further be independently selected from:

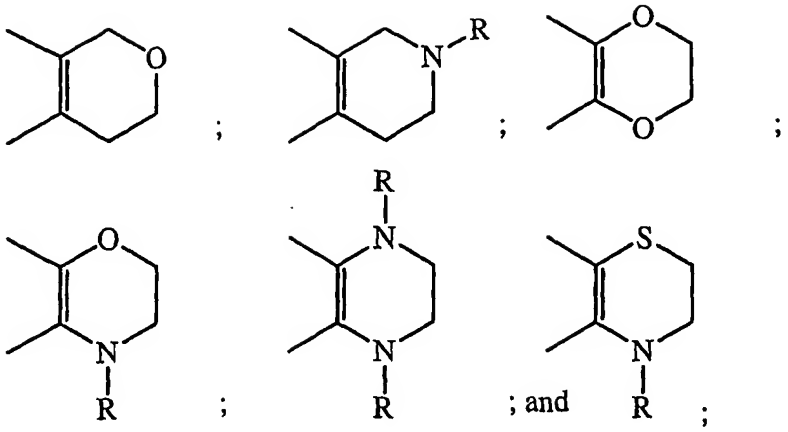
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic

rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 $N(C_1$-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 $N(C_1$-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 $N(C_1$-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and $N(C_1$-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 $N(C_1$-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any $(C_1$-C_6 alkyl$)_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

42. The compound according to Embodiment 41, selected from:

3-Benzofuran-6-ylmethyl-6-[3-(4-chloro-phenyl-prop-1-ynyl]-1-methyl-3,4dihydro-1H-quinolin-2-one;

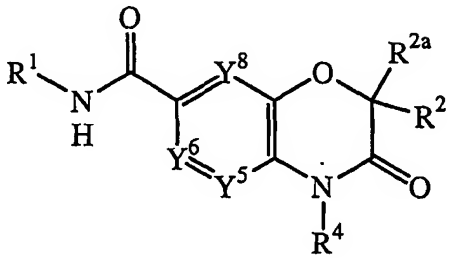
1-Methyl-6-(3-pyrazol-1-yl-prop-1-ynyl)-3-thiophen-2-ylmethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

3-(3-Chlorobenzyl)-1-methyl-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-[1,5]naphthyridin-2-one; and

3-Furan-2-ylmethyl-6-(3-imidazol-1-yl-prop-1-ynyl)-1-methyl-3,4-dihydro-1H-[1,7]naphthyridin-2-one;

or a pharmaceutically acceptable salt thereof.

43. A compound of Formula V



V

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C=C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

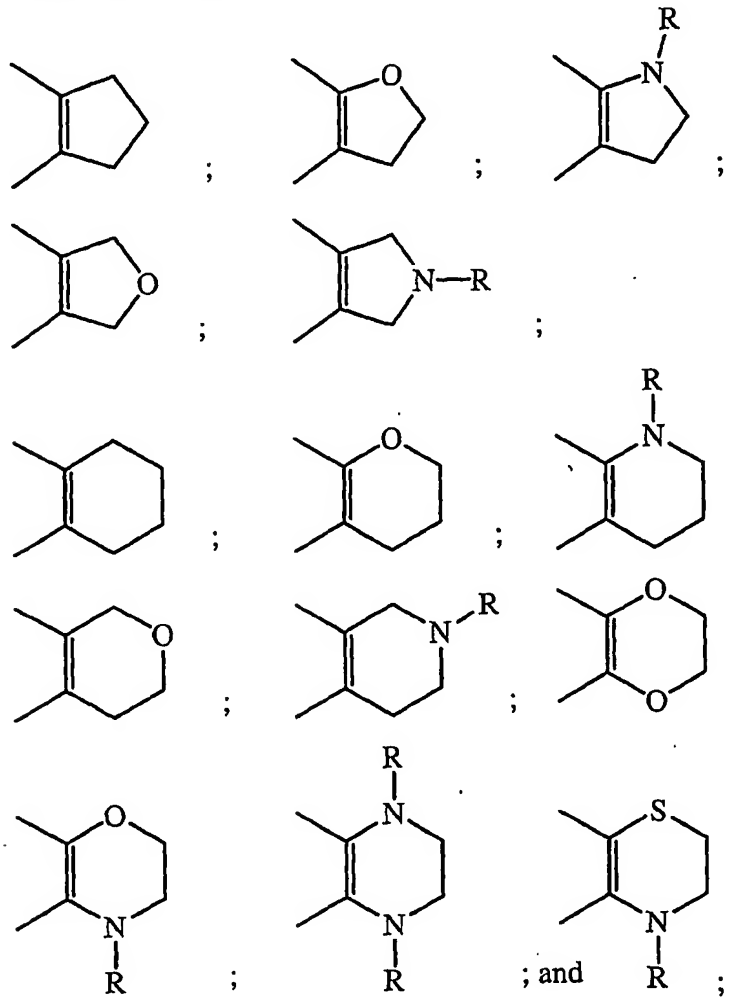
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

44. The compound according to Embodiment 43, selected from:

4-Methyl-3-oxo-2-(4-trifluoromethyl-benzylidene)-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 3-methoxy-benzylamide;

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid benzylamide; and

2-(3-Chloro-4-fluoro-benzyl)-4-methyl-3-oxo3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid (quinolin-3-ylmethyl)-amide;

or a pharmaceutically acceptable salt thereof.

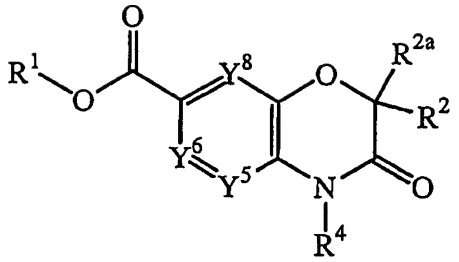
45. The compound according to Embodiment 43, selected from:

3-Benzylidene-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b] [1,4]oxazine-6-carboxylic acid benzylamide; and

4-Methyl-3-oxo-2-thiophen-2-ylmethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carboxylic acid 4-fluoro-benzylamide;

or a pharmaceutically acceptable salt thereof.

46. A compound of Formula VI



VI

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C{=}C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

$(C_1\text{-}C_6$ alkyl)-C(O)O-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl);

$(C_1\text{-}C_6$ alkyl)-N(H)$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)$_2$-$NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl)$_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

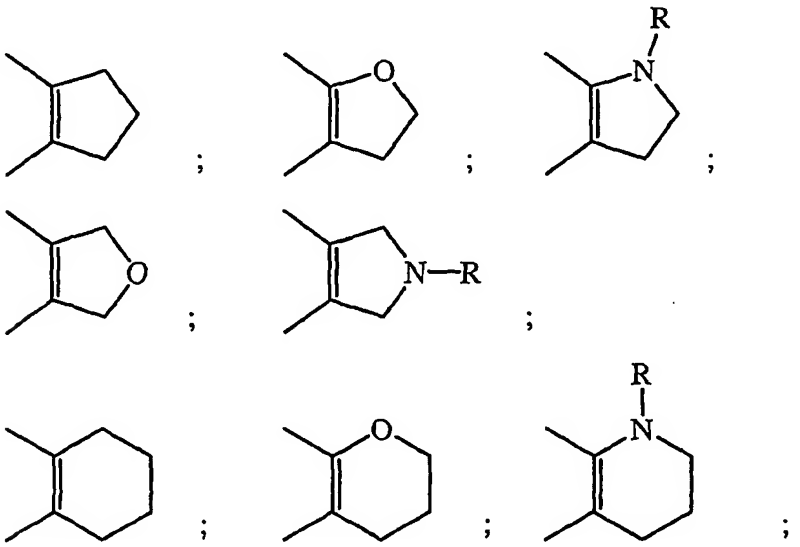
wherein each substituent on a carbon atom may further be independently selected from:

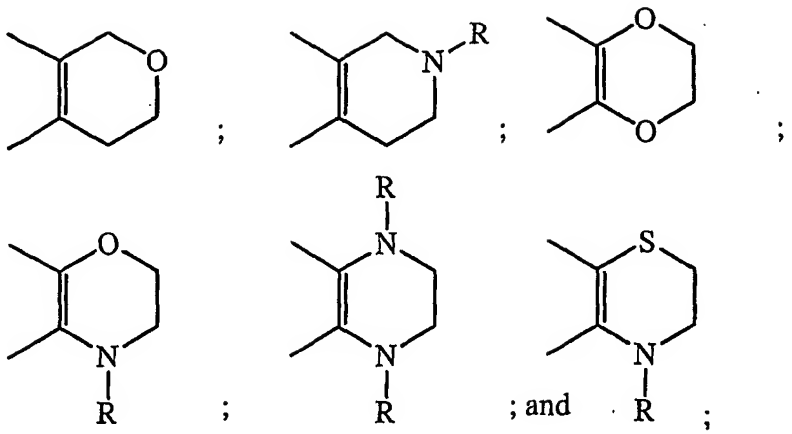
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic

rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

47. The compound according to Embodiment 46, selected from:

4-Methyl-3-oxo-2-(4-trifluoromethyl-benzylidene)-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 3-methoxy-benzyl ester;

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid benzyl ester; and

2-(3-Chloro-4-fluoro-benzyl)-4-methyl-3-oxo3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid (quinolin-3-ylmethyl)-ester;

or a pharmaceutically acceptable salt thereof.

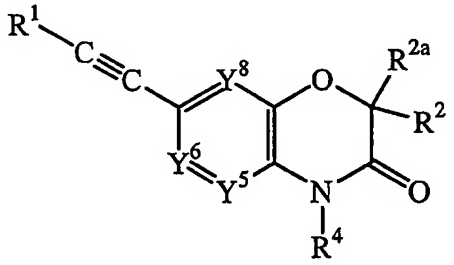
48. The compound according to Embodiment 46, selected from:

3-Benzylidene-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carboxylic acid benzyl ester; and

4-Methyl-3-oxo-2-thiophen-2-ylmethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carboxylic acid 4-fluoro-benzyl ester;

or a pharmaceutically acceptable salt thereof.

49. A compound of Formula VII



VII

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C=C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-(G)$_m$;

Substituted 3- to 6-membered heterocycloalkyl-(G)$_m$;

5- or 6-membered heteroaryl-(G)$_m$;

Substituted 5- or 6-membered heteroaryl-(G)$_m$;

(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

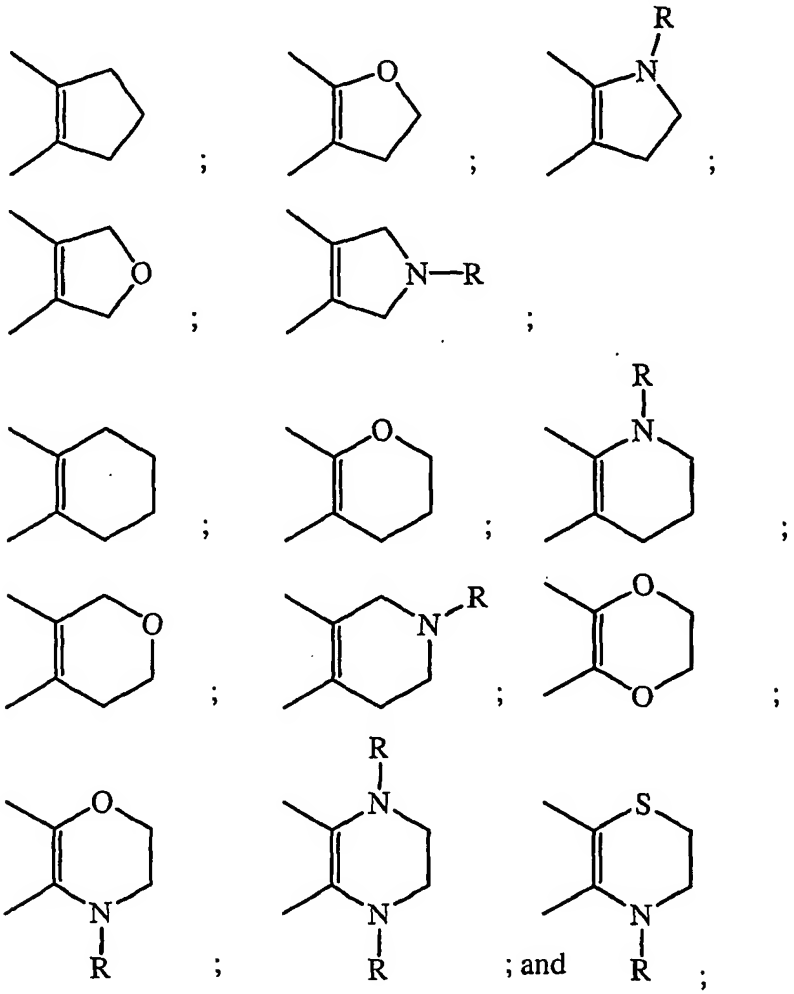
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms

and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

50. The compound according to Embodiment 49, selected from:

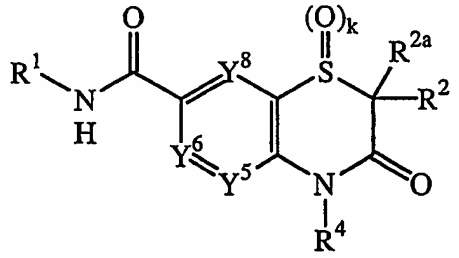
6-[3-(4-Chloro-phenyl)-prop-1-ynyl]-1-methyl-3-pyridin-4-ylmethyl-1H-pyrido[2,3-b][1,4]oxazin-2-one;

4-Methyl-7-(3-pyrazol-1-yl-prop-1-ynyl)-2-thiophen-2-ylmethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one; and

4-[4-Methyl-3-oxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl]-benzoic acid;

or a pharmaceutically acceptable salt thereof.

51. A compound of Formula VIII



VIII

or a pharmaceutically acceptable salt thereof,

wherein:

k is an integer of from 0 to 2;

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C{=}C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl$)_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl$)_m$;

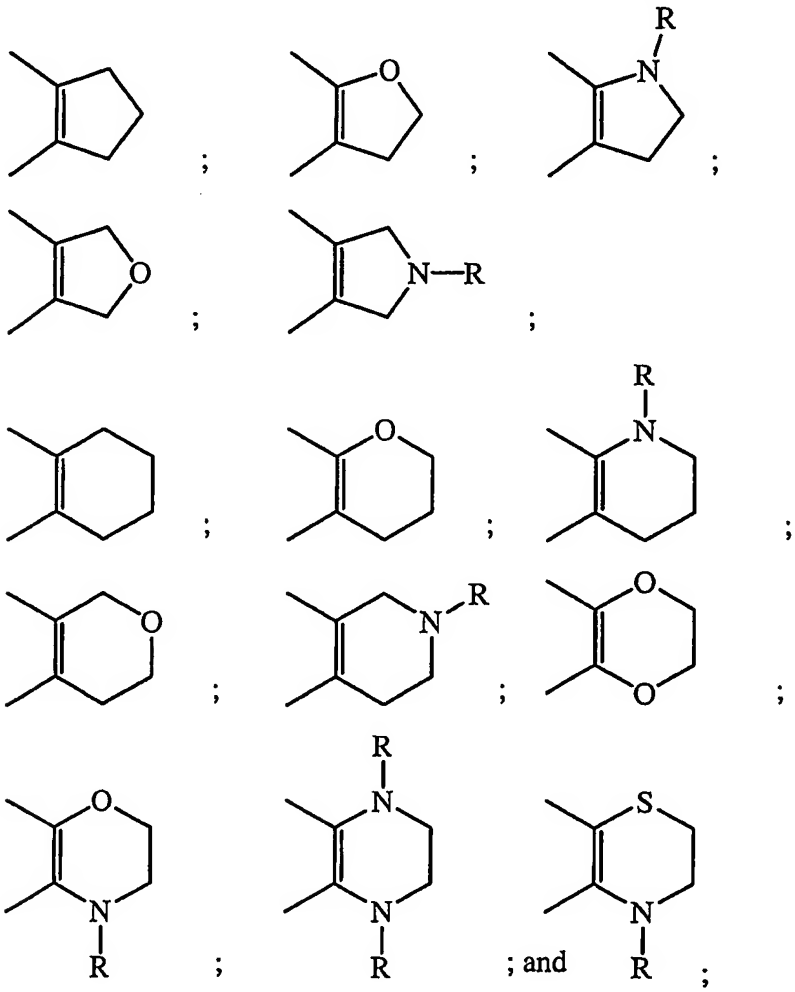
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:



R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

52. The compound according to Embodiment 51, selected from:

4-Methyl-2-(4-methyl-benzylidene)-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-cyano-benzylamide;

2-(4-Chloro-benzyl)-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazone-7-carboxylic acid-benzylamide;

4-Methyl-3-oxo-2-pyridin-3-ylmethyl-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide; and

2-Furan-2-ylmethyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-methoxy-benzylamide;

or a pharmaceutically acceptable salt thereof.

53. The compound according to Embodiment 51, selected from:

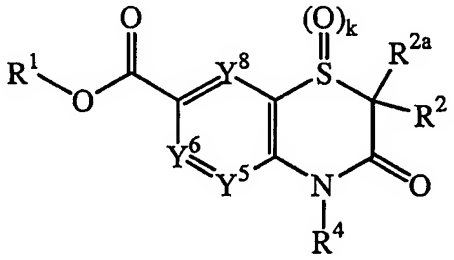
3-(3-Chloro-benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazine-6-carboxylic acid (thiazol-2-ylmethyl)-amide;

2-Furan-2-ylmethylene-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide; and

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-7-carboxylic acid 3-methoxy-benzylamide;

or a pharmaceutically acceptable salt thereof.

54. A compound of Formula IX



IX

or a pharmaceutically acceptable salt thereof,

wherein:

k is an integer of from 0 to 2;

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C=C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-(C_1-C_8 alkylenyl);

(C_1-C_6 alkyl)-N(H)$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

(C_1-C_6 alkyl)$_2$-$NS(O)_2$-(C_1-C_8 alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-(G)$_m$;

Substituted 3- to 6-membered heterocycloalkyl-(G)$_m$;

5- or 6-membered heteroaryl-(G)$_m$;

Substituted 5- or 6-membered heteroaryl-(G)$_m$;

(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$; and

(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$;

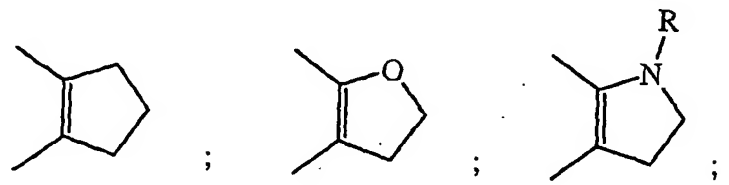
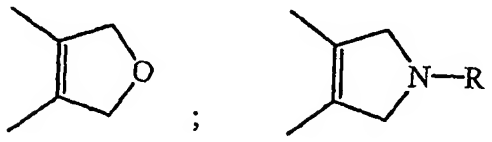
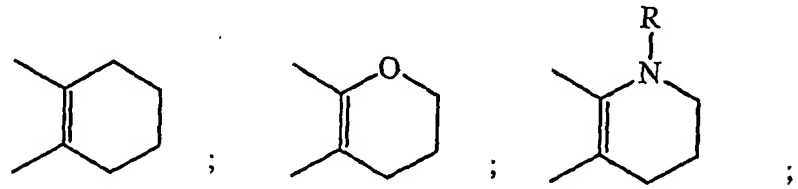
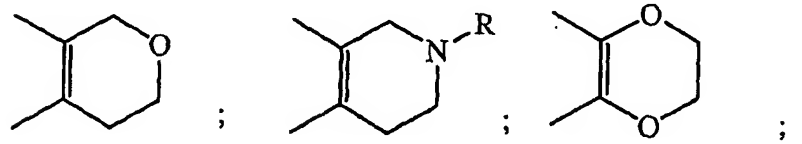
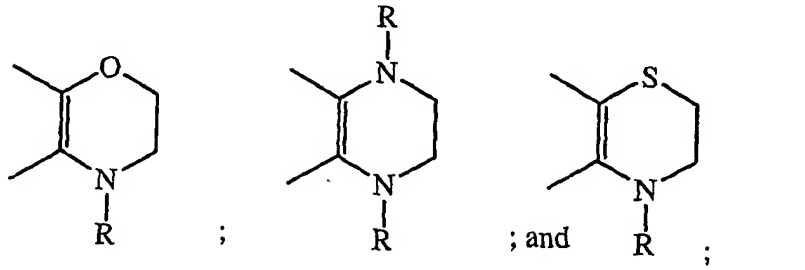
wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:

R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH{=}CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

55. The compound according to Embodiment 54, selected from:

4-Methyl-2-(4-methyl-benzylidene)-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-cyano-benzyl ester;

2-(4-Chloro-benzyl)-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazone-7-carboxylic acid-benzyl ester;

4-Methyl-3-oxo-2-pyridin-3-ylmethyl-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-ester; and

2-Furan-2-ylmethyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-methoxy-benzyl ester;

or a pharmaceutically acceptable salt thereof.

56. The compound according to Embodiment 54, selected from:

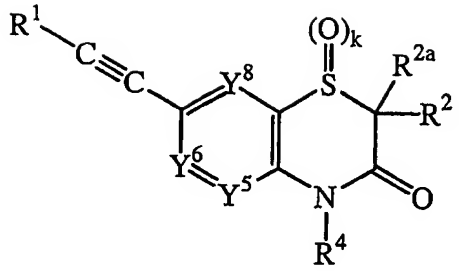
3-(3-Chloro-benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazine-6-carboxylic acid (thiazol-2-ylmethyl)-ester;

2-Furan-2-ylmethylene-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-ester; and

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-7-carboxylic acid 3-methoxy-benzyl ester;

or a pharmaceutically acceptable salt thereof.

57. A compound of Formula X



X

or a pharmaceutically acceptable salt thereof,

wherein:

k is an integer of from 0 to 2;

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C{=}C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

(C_1-C_6 alkyl)-N(H);

$(C_1\text{-}C_6$ alkyl$)_2$-N;

$(C_1\text{-}C_6$ alkyl$)$-C(O)O-$(C_1\text{-}C_8$ alkylenyl$)_m$;

$(C_1\text{-}C_6$ alkyl$)$-C(O)O-(1- to 8-membered heteroalkylenyl$)_m$;

$(C_1\text{-}C_6$ alkyl$)$-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl$)_m$;

$(C_1\text{-}C_6$ alkyl$)$-C(O)N(H)-(1- to 8-membered heteroalkylenyl$)_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl$)$;

$(C_1\text{-}C_6$ alkyl$)$-N(H)$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl$)_m$;

$(C_1\text{-}C_6$ alkyl$)_2$-$NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl$)_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl$)$-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl$)_m$; and

$(C_1\text{-}C_6$ alkyl$)$-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl$)_m$;

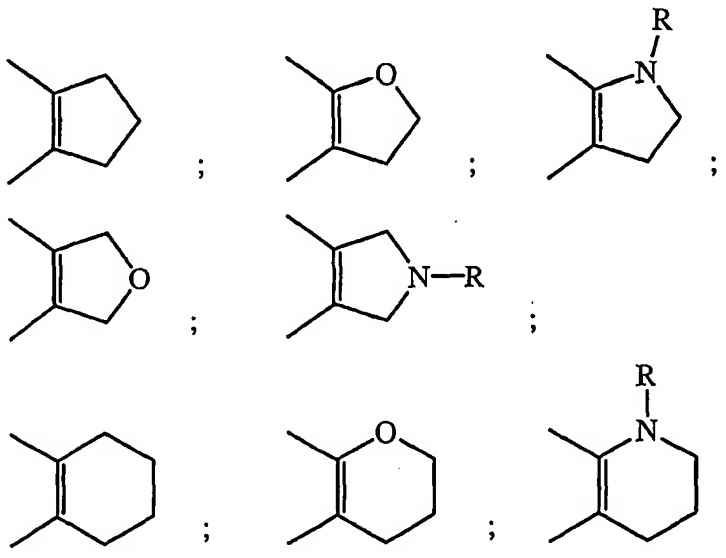
wherein each substituent on a carbon atom may further be independently selected from:

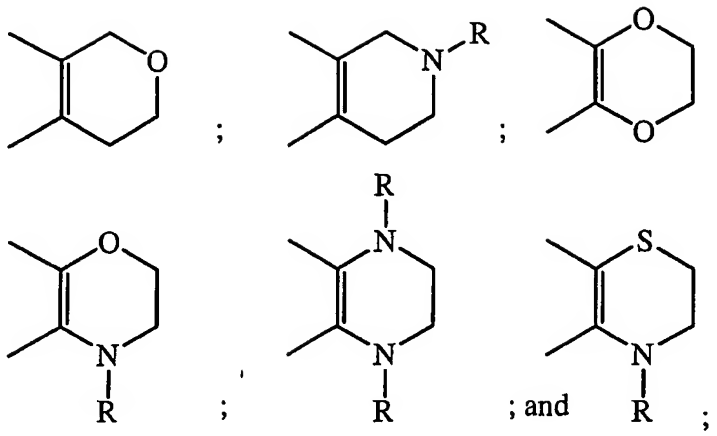
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic

rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

58. The compound according to Embodiment 57, selected from:

3-(3-Chloro-benzyl)-methyl-6-(3-phenyl-prop-1-ynyl)-1H-pyrido[2,3-b][1,4]thiazin-2-one;

2-Furan-2-ylmethyl-7-(3-imidazol-1-yl-prop-1-ynyl)-4-methyl-4H-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-7-(3-[1,2,4]triazol-1-yl-prop-1-ynyl)-4H-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-7-phenylethynyl-4H-pyrido[3,2-b][thiazin-3-one; and

2-(4-Methanesulfonyl-benzyl)-4-methyl-7-(3-pyridin-3-yl-prop-1-ynyl)-4H-benzo[1,4]thiazin-3-one;

or a pharmaceutically acceptable salt thereof.

59. The compound according to Embodiment 57, selected from:

3-(3-Chloro-benzyl)-1-methyl-4,4-dioxo-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-4λ^6-pyrido[2,3-b][1,4]thiazin-2-one;

2-Furan-2-ylmethyl-7-(3-imidazol-1-yl-prop-1-ynyl)-4-methyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-1,1-dioxo-7-(3-[1,2,4]triazol-1-yl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-1,1-dioxo-7-phenylethynyl-1,4-dihydro-2H-1λ^6-pyrido[3,2-b][thiazin-3-one; and

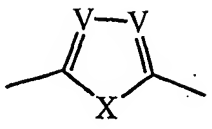
2-(4-Methanesulfonyl-benzyl)-4-methyl-1,1-dioxo-7-(3-pyridin-3-yl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one;

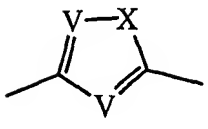
or a pharmaceutically acceptable salt thereof.

60. The compound according to any one of Embodiments 51, 54, and 57, wherein k is 2.

61. The compound according to any one of Embodiments 51, 54, and 57, wherein k is 1.

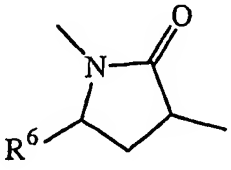
62. The compound according to Embodiment 1, wherein Q is



; or 

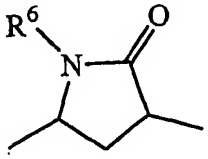
, wherein V and X are as defined above.

63. The compound according to Embodiment 1, wherein Q is



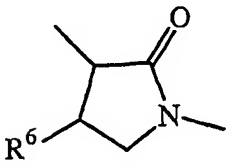
, wherein R^6 is as defined above.

64. The compound according to Embodiment 1, wherein Q is



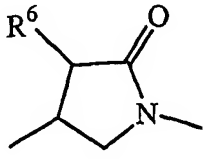
, wherein R^6 is as defined above.

65. The compound according to Embodiment 1, wherein Q is



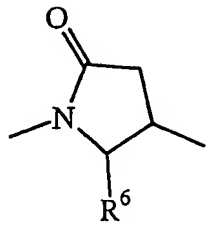
, wherein R^6 is as defined above.

66. The compound according to Embodiment 1, wherein Q is selected from:



, wherein R^6 is as defined above.

67. The compound according to Embodiment 1, wherein Q is selected from:



, wherein R^6 is as defined above.

68. A pharmaceutical composition, comprising a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

69. The pharmaceutical composition according to Embodiment 68, comprising a compound of Formula I according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

70. A method for inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

71. The method according to Embodiment 70, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

72. A method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

73. The method according to Embodiment 72, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

74. A method for treating arthritis, comprising administering to a patient suffering from an arthritis disease a nontoxic antiarthritic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

75. The method according to Embodiment 74, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

76. A method for treating osteoarthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

77. The method according to Embodiment 76, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

78. A method for treating rheumatoid arthritis, comprising administering to a patient suffering from rheumatoid arthritis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

79. The method according to Embodiment 78, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

80. A method for treating psoriatic arthritis, comprising administering to a patient suffering from psoriatic arthritis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

81. The method according to Embodiment 80, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

82. A method for treating a cancer, comprising administering to a patient suffering from a cancer a nontoxic anti-cancer effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

83. The method according to Embodiment 82, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

84. A method for treating breast carcinoma, comprising administering to a patient suffering from breast carcinoma a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

85. The method according to Embodiment 84, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

86. A method for treating atherosclerosis, comprising administering to a patient suffering from atherosclerosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

87. The method according to Embodiment 86, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

88. A method for treating inflammation, comprising administering to a patient suffering from inflammation a nontoxic effective amount of a compound of

Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

89. The method according to Embodiment 88, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

90. A method for treating heart failure, comprising administering to a patient suffering from heart failure a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

91. The method according to Embodiment 90, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

92. A method for treating age-related macular degeneration, comprising administering to a patient suffering from age-related macular degeneration a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

93. The method according to Embodiment 92, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

94. A method for treating chronic obstructive pulmonary disease, comprising administering to a patient suffering from chronic obstructive pulmonary disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

95. The method according to Embodiment 94, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

96. A method for treating heart disease, comprising administering to a patient suffering from heart disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

97. The method according to Embodiment 96, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

98. A method for treating multiple sclerosis, comprising administering to a patient suffering from multiple sclerosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

99. The method according to Embodiment 98, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

100. A method for treating psoriasis, comprising administering to a patient suffering from psoriasis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

101. The method according to Embodiment 100, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

102. A method for treating asthma, comprising administering to a patient suffering from asthma a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

103. The method according to Embodiment 102, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

104. A method for treating cardiac insufficiency, comprising administering to a patient suffering from cardiac insufficiency a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

105. The method according to Embodiment 104, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

106. A method for treating inflammatory bowel disease, comprising administering to a patient suffering from inflammatory bowel disease a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

107. The method according to Embodiment 106, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

108. A method for treating osteoporosis, comprising administering to a patient suffering from osteoporosis a nontoxic effective amount of a compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

109. The method according to Embodiment 108, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

110. A method for treating periodontal diseases, comprising administering to a patient suffering from periodontal diseases a nontoxic effective amount of a

compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof.

111. The method according to Embodiment 110, wherein the compound of Formula I is according to any one of Embodiments 2 to 67, or a pharmaceutically acceptable salt thereof.

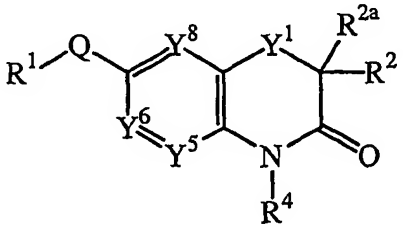
112. The method according to any one of Embodiments 70 to 111, wherein the compound of Formula I according to Embodiment 1, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition according to Embodiment 68 or 69.

113. The compound according to Embodiment 1, wherein Y^6 is N and Q is N(H)C(O).

114. The compound according to Embodiment 1, wherein Y^8 is N and Q is N(H)C(O).

DETAILED DESCRIPTION OF THE INVENTION

This invention provides compounds defined by Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein R^1, Q, Y^1, Y^5, Y^6, Y^8, R^2, R^{2a}, and R^4 are as defined above.

The invention also provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, as defined above, together with a pharmaceutically acceptable carrier, diluent, or excipient.

The invention also provides methods of inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides methods of treating a disease mediated by an MMP-13 enzyme in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition.

The invention also provides methods of treating diseases such as heart disease, multiple sclerosis, osteo- and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, cardiac insufficiency, inflammatory bowel disease, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof, either alone or in a pharmaceutical composition.

The invention also provides combinations, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with another pharmaceutically active component as described.

As seen above, the groups of Formula I include "C_1-C_6 alkyl" groups. C_1-C_6 alkyl groups are straight and branched carbon chains having from 1 to 6 carbon atoms. Examples of C_1-C_6 alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, and 1-hexyl.

The phrase "substituted C_1-C_6 alkyl" means a C_1-C_6 alkyl group as defined above that is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_1-C_6 alkyl groups include CH_2OH, CF_2OH, $CH_2C(CH_3)_2CO_2CH_3$, CF_3, $C(O)CF_3$, $C(O)$-CH_3, $(CH_2)_4$-S-CH_3, $CH(CO_2H)CH_2CH_2C(O)NMe_2$, $(CH_2)_5NH$-$C(O)$-NH_2, CH_2-CH_2-C(H)-(4-fluorophenyl), $CH(OCH_3)CH_2CH_3$, $CH_2SO_2NH_2$, and $CH(CH_3)CH_2CH_2OC(O)CH_3$.

The term "C_2-C_6 alkenyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 6 carbon atoms and 1 or 2 carbon-carbon double bonds, and include allenyl groups. Typical examples of C_2-C_6 alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-3-yl, 2-penten-2-yl, and 1-hexen-6-yl.

The phrase "substituted C_2-C_6 alkenyl" means a C_2-C_6 alkenyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_2-C_6 alkenyl groups include $C(H)=C(H)CH_2OH$, $CH=CF_2$, $CH_2C(H)=C(H)-(CH_2)_2CF_2OH$, $CH_2C(=CH_2)CO_2CH_3$, $C(H)=C(H)-CF_3$, $CH_2-CH_2-C(H)=C(H)-C(O)-CH_3$, $C(H)=C(CH_3)-S-CH_3$, $C(H)=C(H)-C(H)=C(CH_3)-CO_2Me$, and $C(H)=C=C(H)OC(O)CH_3$.

The term "C_2-C_6 alkynyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 6 carbon atoms and 1 or 2 carbon-carbon triple bonds. Typical examples of C_2-C_6 alkynyl groups include ethenyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyn-3-yl, 2-pentyn-1-yl, and 1-hexyn-6-yl.

The phrase "substituted C_2-C_6 alkynyl" means a C_2-C_6 alkynyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_2-C_6 alkynyl groups include $C\equiv CCH_2OH$, $C\equiv CF$, $CH_2C\equiv C-(CH_2)_2CF_2OH$, $C\equiv C-CH_2CO_2CH_3$, $CH_2C\equiv C-CF_3$, $CH_2-CH_2-C\equiv C-C(O)-CH_3$, $C\equiv C-S-CH_3$, and $C\equiv C-C(O)OC(O)CH_3$.

The term "C_3-C_6 cycloalkyl" means an unsubstituted cyclic hydrocarbon group having from 3 to 6 carbon atoms. C_3-C_6 cycloalkyl may optionally contain one carbon-carbon double bond. The group C_3-C_6 cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclopenten-1-yl, cyclopenten-4-yl, and cyclohexyl.

The phrase "substituted C_3-C_6 cycloalkyl" means a C_3-C_6 cycloalkyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted C_3-C_6 cycloalkyl

groups include 1-hydroxy-cyclopropyl, cyclobutanon-3-yl, 3-(3-phenyl-ureido)-cyclopent-1-yl, and 4-carboxy-cyclohexyl.

The phrase "3- to 6-membered heterocycloalkyl" means an unsubstituted saturated cyclic group having carbon atoms and 1 or 2 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 2 N(H), and 2 $N(C_1\text{-}C_6$ alkyl), wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other. Optionally, a 3- to 6-membered heterocycloalkyl may contain one carbon-carbon or carbon-nitrogen double bond. Illustrative examples of 3- to 6-membered heterocycloalkyl includes aziridin-1-yl, 1-oxa-cyclobutan-2-yl, tetrahyrdofuran-3-yl, morpholin-4-yl, 2-thiacyclohex-1-yl, 2-oxo-2-thiacyclohe-1-yl, 2,2-dioxo-2-thiacyclohex-1-yl, and 4-methyl-piperazin-2-yl.

The phrase "substituted 3- to 6-membered heterocycloalkyl" means a 3- to 6-membered heterocycloalkyl as defined above, which is substituted with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted 3- to 6-membered heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, and 1-cyclopropyl-4-methyl-piperazin-2-yl.

The term "C_1-C_8 alkylenyl" means a saturated hydrocarbon diradical that is straight or branched and has from 1 to 8 carbon atoms. C_1-C_8 alkylenyl having from 2 to 8 carbon atoms may optionally independently contain one carbon-carbon double bond. Illustrative examples of C_1-C_8 alkylenyl include CH_2, CH_2CH_2, $C(CH_3)H$, $C(H)(CH_3)CH_2CH_2$, and $CH_2C(H)=C(H)CH_2CH_2CH_2CH_2CH_2$.

The term "1- to 8-membered heteroalkylenyl" means a saturated diradical chain that is straight or branched and contains from 1 to 7 carbon atoms and 1 heteroatom selected from O, S, N(H), and $N(C_1\text{-}C_6$ alkyl). 2- to 8-membered heteroalkylenyl, having from 2 to 8 chain atoms, may optionally independently contain one carbon-carbon double bond. Illustrative examples of 1- to 8-membered heteroalkylenyl include OCH_2, CH_2CH_2O, $C(CH_3)HS$, and $CH_2C(H)=C(H)CH_2N(H)CH_2CH_2CH_2$.

The phrase "C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl)" means a C_3-C_6 cycloalkyl, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above. Illustrative examples of C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl include cyclopropylmethyl, 1-cyclopentyl-hex-2-yl, and 2-cyclobutyl-but-2-yl.

The phrase "Substituted C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl)" means a C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl), as defined above, substituted on C_3-C_6 cycloalkyl and/or C_1-C_8 alkylenyl with from 1 to 4 substituents, as defined above. Illustrative examples of substituted C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl include cyclopropylcarbonyl and 1-(1-aminomethyl-cyclopentyl)-hex-2-yl.

The phrase "C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl)" means a cyclopentyl or cyclohexyl bonded through a C_1-C_8 alkylenyl, as defined above, wherein the cycloalkyl optionally contains 1 carbon-carbon double bond.

The phrase "Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl)" means a substituted cyclopentyl or cyclohexyl, wherein the substituents are as defined above, bonded through a C_1-C_8 alkylenyl, as defined above, wherein the cycloalkyl optionally contains 1 carbon-carbon double bond.

The phrase "C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl)" means a cyclopentyl or cyclohexyl fused to another cyclopentyl or cyclohexyl to give a 5,5-, 5,6-, or 6,6-fused bicyclic carbocyclic group, which is bonded through a C_1-C_8 alkylenyl, as defined above, wherein the bicycloalkyl optionally contains 1 carbon-carbon double bond.

The phrase "Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl)" means a C_8-C_{10} bicycloalkyl, as defined above, substituted with from 1 to 4 substituents, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl)" means a 5- or 6-membered ring containing carbon atoms and 1 or 2 heteroatoms selected from 1 O, 1 S, 1 N, 2 N(H), and 2 N(C_1-C_6 alkyl), bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_6 alkylenyl)" means a 5- or 6-membered heterocycloalkyl, as defined above, substituted with from 1 to 4 substituents, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl)" means a 5- or 6-membered ring fused to another 5- or 6-membered ring to give a 5,5-, 5,6-, or 6,6-fused bicyclic group containing carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), bonded through a C_1-C_8 alkylenyl, as defined above, wherein the bicycloalkyl optionally contains 1 carbon-carbon double bond or 1 carbon-nitrogen double bond.

The phrase "Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_6 alkylenyl)" means an 8- to 10-membered heterobicycloalkyl, as defined above, substituted with from 1 to 4 substituents, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl)" means a 3- to 6-membered heterocycloalkyl, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl)" means a substituted 3- to 6-membered heterocycloalkyl, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "Phenyl-(C_1-C_8 alkylenyl)" means a phenyl group bonded through a C_1-C_8 alkylenyl diradical, wherein C_1-C_8 alkylenyl is as defined above. Illustrative examples of phenyl-(C_1-C_8 alkylenyl) include benzyl, 2-phenylethyl, 1-phenyl-prop-1-yl, and 3-phenyl-heptyl.

The phrase "Substituted phenyl-(C_1-C_8 alkylenyl)" means a phenyl-(C_1-C_8 alkylenyl) as defined above, which is substituted on phenyl and/or C_1-C_8 alkylenyl with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted phenyl-(C_1-C_8 alkylenyl) include 4-fluoro-phenylmethyl, 2-(4-carboxy-phenyl)-ethyl, 1-(2,4-dimethoxy-phenyl)-2-oxo-propyl, and 1-phenyl-5,5-difluoro-oct-3-yl.

The term "naphthyl" includes 1-naphthyl and 2-napthyl.

The phrase "Naphthyl-(C_1-C_8 alkylenyl)" means a naphthyl group as defined above bonded through a C_1-C_8 alkylenyl diradical, wherein C_1-C_8 alkylenyl is as defined above. Illustrative examples of naphthyl-(C_1-C_8 alkylenyl) include naphth-1-ylmethyl, 2-(naphth-1-yl)ethyl, and 3-(naphth-2-yl)-l-heptyl.

The phrase "Substituted naphthyl-(C_1-C_8 alkylenyl)" means a naphthyl-(C_1-C_8 alkylenyl) as defined above, which is substituted on naphthyl and/or C_1-C_8 alkylenyl with from 1 to 4 substituents independently selected from the list above. Illustrative examples of substituted phenyl-(C_1-C_8 alkylenyl) include 4-fluoro-(naphth-1-yl)methyl, 2-(4-carboxy-(naphth-1-yl))-ethyl, 1-(2,4-dimethoxy-(naphth-1-yl))-2-oxo-propyl, and 1-(naphth-2-yl)-5,5-difluorohept-2-yl.

The phrase "5- or 6-membered heteroaryl" means a 5-membered, monocyclic heteroaryl having carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, or a 6-membered, monocyclic heteroaryl having carbon atoms and 1 or 2 heteroatoms selected from 2 N, and wherein:

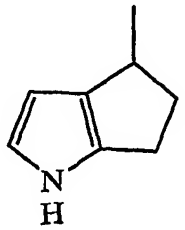
(i) The phrase "5-membered, monocyclic heteroaryl" means a 5-membered, monocyclic, aromatic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 5-membered, monocyclic heteroaryl include thiophen-2-yl, furan-2-yl, pyrrol-3-yl, pyrrol-1-yl, imidazol-4-yl, isoxazol-3-yl, oxazol-2-yl, thiazol-4-yl, tetrazol-1-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-triazol-1-yl, and pyrazol-3-yl; and

(ii) The phrase "6-membered, monocyclic heteroaryl" means a 6-membered, monocyclic, aromatic ring group as defined above having carbon atoms and 1 or 2 N. Illustrative examples of a 6-membered, monocyclic heteroaryl include pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyridazin-4-yl, and pyrazin-2-yl.

The phrase "8- to 10-membered heterobiaryl" means an 8-membered, 5,5-fused bicyclic heteroaryl, a 9-membered, 6,5-fused bicyclic heteroaryl, or a 10-membered, 6,6-fused bicyclic heteroaryl, having carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, wherein at least one of the 2 fused rings is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other, which are as defined below:

(iii) The phrase "8-membered, 5,5-fused bicyclic heteroaryl" means a an 8-membered aromatic, fused-bicyclic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-

C_6 alkyl), and 4 N. Illustrative examples of an 8-membered, fused-bicyclic heteroaryl include



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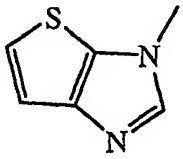

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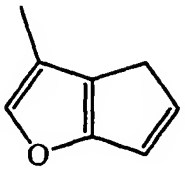

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(iv) The phrase "9-membered, 6,5-fused bicyclic heteroaryl" means a 9-membered aromatic, fused-bicyclic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 9-membered, fused-bicyclic heteroaryl include indol-2-yl, indol-6-yl, iso-indol-2-yl, benzimidazol-2-yl, benzimidazol-1-yl, benztriazol-1-yl, benztriazol-5-yl, benzoxazol-2-yl, benzothiophen-5-yl, and benzofuran-3-yl; and

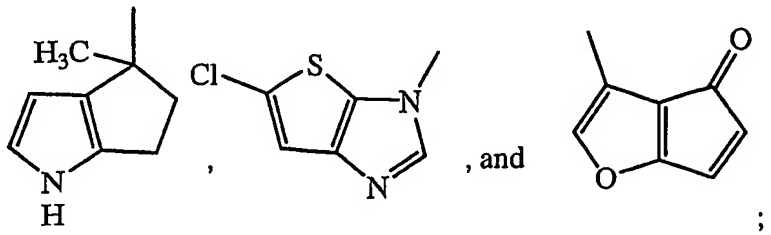
(v) The phrase "10-membered, 6,5-fused bicyclic heteroaryl" means a 10-membered aromatic, fused-bicyclic ring group as defined above having carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N. Illustrative examples of a 10-membered, fused-bicyclic heteroaryl include quinolin-2-yl, isoquinolin-7-yl, and benzopyrimidin-2-yl.

The phrases "substituted 5- or 6-membered heteroaryl" and "substituted 8- to 10-membered heterobiaryl" means a 5- or 6-membered heteroaryl, as defined above, or an 8- to 10-membered heterobiaryl, as defined above, respectively, which is substituted on a carbon (CH) atom, and/or nitrogen [N(H)] atom in the case of 5-, 8- to 10-membered heterobiaryl, with from 1 to 4 substituents independently selected from the list above.

Illustrative examples of substituted 5-membered, monocyclic heteroaryl groups include 2-hydroxy-oxoazol-4-yl, 5-chloro-thiophen-2-yl, 1-methylimidazol-5-yl, 1-propyl-pyrrol-2-yl, 1-acetyl-pyrazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, and 2-hexyl-tetrazol-5-yl.

Illustrative examples of substituted 6-membered, monocyclic heteroaryl groups include 4-acetyl-pyridin-2-yl, 3-fluoro-pyridin-4-yl, 5-carboxy-pyrimidin-2-yl, 6-tertiary butyl-pyridazin-4-yl, and 5-hdyroxymethyl-pyrazin-2-yl.

Illustrative examples of substituted 8-membered, 5,5-fused bicyclic heteroaryl include:



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Illustrative examples of substituted 9-membered, 5,6-fused bicyclic heteroaryl include 3-(2-aminomethyl)-indol-2-yl, 2-carboxy-indol-6-yl, 1-(methanesulfonyl)-iso-indol-2-yl, 5-trifluorometyl-6,7-difluoro-4-hydroxymethyl-benzimidazol-2-yl, 4-(3-methylureido)-2-cyano-benzimidazol-1-yl, 1-methylbenzimidazol-6-yl, 1-acetylbenztriazol-7-yl, 1-methanesulfonyl-indol-3-yl, 1-cyano-6-aza-indol-5-yl, and 1-(2,6-dichlorophenylmethyl)-benzpyrazol-3-yl.

Illustrative examples of substituted 10-membered, 6,6-fused bicyclic heteroaryl include 5,7-dichloro-quinolin-2-yl, isoquinolin-7-yl-1-carboxylic acid ethyl ester, and 3-bromo-benzopyrimidin-2-yl.

The phrase "5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)" means a 5- or 6-membered heteroaryl, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl)" means a 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl), as defined above, which is substituted on 5- or 6-membered heteroaryl and/or C_1-C_8 alkylenyl with from 1 to 4 substituents independently selected from the list above.

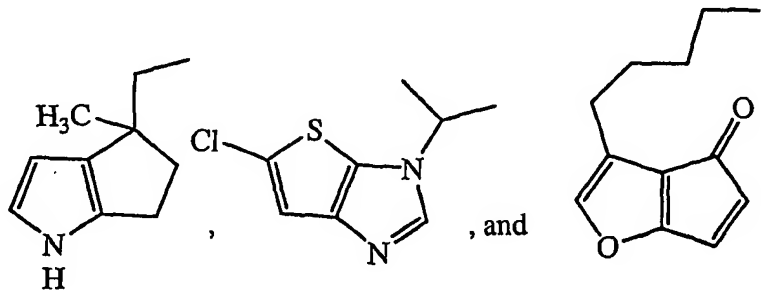
Illustrative examples of substituted 5-membered heteroaryl-(C_1-C_8 alkylenyl) groups include 2-hydroxy-oxoazol-4-ylmethyl, 4-(5-chloro-thiophen-2-yl)-hex-1-yl, and 2-tetrazol-5-yloctyl.

Illustrative examples of substituted 6-membered heteroaryl-(C_1-C_8 alkylenyl) groups include 4-acetyl-pyridin-2-ylmethyl, 7-(3-fluoro-pyridin-4-yl)-hept-2-yl, and 2-(5-hdyroxymethyl-pyrazin-2-yl)-1,1-difluoro-2-hydroxy-prop-2-yl.

The phrase "8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)" means an 8- to 10-membered heterobiaryl, as defined above, bonded through a C_1-C_8 alkylenyl, as defined above.

The phrase "Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl)" means an 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl), as defined above, which is substituted on 8- to 10-membered heterobiaryl and/or C_1-C_8 alkylenyl with from 1 to 4 substituents independently selected from the list above.

Illustrative examples of substituted 8-membered heterobiaryl-(C_1-C_8 alkylenyl) include:



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Illustrative examples of substituted 9-membered heterobiaryl-(C_1-C_8 alkylenyl) include 3-(2-aminomethyl)-indol-2-ylmethyl, and 1-(1-(2,6-dichlorophenylmethyl)-benzpyrazol-3-yl)-prop3-yl.

Illustrative examples of substituted 10-membered heterobiaryl-(C_1-C_8 alkylenyl) include 5,7-dichloro-quinolin-2-ylmethyl, and 5-(3-bromo-benzopyrimidin-2-yl)-oct-2-yl.

The phrase "(C_1-C_6 alkyl)-O" means a C_1-C_6 alkyl group, as defined above, bonded through an oxygen atom.

The phrase "(C_1-C_6 alkyl)-S" means a C_1-C_6 alkyl group, as defined above, bonded through an sulfur atom.

The phrase "(C_1-C_6 alkyl)-$S(O)_2$" means a C_1-C_6 alkyl group, as defined above, bonded through a sulfur atom, which sulfur atom is substituted with two oxygen atoms.

The phrase "(C_1-C_6 alkyl)-N(H)" means a C_1-C_6 alkyl group, as defined above, bonded through a nitrogen atom, which is bonded to a hydrogen atom.

The phrase "(C_1-C_6 alkyl)$_2$-N" means two independently selected C_1-C_6 alkyl groups, as defined above, including cyclic groups wherein the two C_1-C_6

alkyl groups are taken together with the nitrogen atom to which they are both bonded to form a 5- or 6-membered heterocycloalkyl, bonded through a nitrogen atom.

The phrase "(C_1-C_6 alkyl)-OC(O)" means a C_1-C_6 alkyl, as defined above, bonded through an oxygen atom-carbonyl carbon atom.

The phase "(C_1-C_6 alkyl)-C(O)O-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means when, m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-oxygen atom, and, when m is 1, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-oxygen atom-(C_1-C_8 alkylenyl), wherein C_1-C_8 alkylenyl is as defined above.

The phase "(C_1-C_6 alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-oxygen atom, and, when m is 1, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-oxygen atom-(1- to 8-membered heteroalkylenyl), wherein 1- to 8-membered heteroalkylenyl is as defined above.

The phase "(C_1-C_6 alkyl)-C(O)N(H)-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-nitrogen atom, which is bonded to a hydrogen atom, and, when m is 1, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-nitrogen atom-(C_1-C_8 alkylenyl), wherein C_1-C_8 alkylenyl is as defined above and the nitrogen atom is bonded to a hydrogen atom.

The phase "(C_1-C_6 alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$", wherein m is an integer of 0 or 1, means when, m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-nitrogen atom, which is bonded to a hydrogen atom, and, when m is 1, a C_1-C_6 alkyl group, as defined above, bonded through a carbonyl carbon atom-nitrogen atom-(1- to 8-membered heteroalkylenyl), wherein 1- to 8-membered heteroalkylenyl is as defined above and the nitrogen atom is bonded to a hydrogen atom.

The phrase "$H_2NS(O)_2$-(C_1-C_8 alkylenyl)" means an amino bonded through a sulfur atom-(C_1-C_8 alkylenyl), wherein the C_1-C_8 alkylenyl is as defined above and the sulfur atom is bonded to two oxygen atoms.

The phrase "(C_1-C_6 alkyl)-N(H)S(O)$_2$-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a C_1-C_6 alkyl, as defined above, bonded through a nitrogen atom-sulfur atom, and, when m is 1, a C_1-C_6 alkyl, as defined above, bonded through a nitrogen atom-sulfur atom-(C_1-C_8 alkylenyl), wherein the nitrogen atom is bonded to a hydrogen atom, the sulfur atom is bonded to two oxygen atoms, and C_1-C_8 alkylenyl is as defined above.

The phrase "(C_1-C_6 alkyl)$_2$-NS(O)$_2$-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, two C_1-C_6 alkyl groups, as defined above, including cyclic groups wherein the two C_1-C_6 alkyl groups are taken together with the nitrogen atom to which they are both bonded to form a 5- or 6-membered heterocycloalkyl, each bonded through a nitrogen atom-sulfur atom, and, when m is 1, two C_1-C_6 alkyl groups, as defined above, each bonded through a nitrogen atom-sulfur atom-(C_1-C_8 alkylenyl), wherein the nitrogen atom is bonded to a hydrogen atom, the sulfur atom is bonded to two oxygen atoms, and C_1-C_8 alkylenyl is as defined above.

The phrase "3- to 6-membered heterocycloalkyl-(G)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a 3- to 6-membered heterocycloalkyl, as defined above, and, when m is 1, a 3- to 6-membered heterocycloalkyl, as defined above, bonded through a group G, as defined above.

The phrase "Substituted 3- to 6-membered heterocycloalkyl-(G)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a substituted 3- to 6-membered heterocycloalkyl, as defined above, and, when m is 1, a substituted 3- to 6-membered heterocycloalkyl, as defined above, bonded through a group G, as defined above.

The phrase "5- or 6-membered heteroaryl-(G)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a 5- or 6-membered heteroaryl, as defined above, and, when m is 1, a 5- or 6-membered heteroaryl, as defined above, bonded through a group G, as defined above.

The phrase "Substituted 5- or 6-membered heteroaryl-(G)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a substituted 5- or 6-membered heteroaryl, as defined above, and, when m is 1, a substituted 5- or 6-membered heteroaryl, as defined above, bonded through a group G, as defined above.

The term "Phenyl-O-(C_1-C_8 alkylenyl)" means a phenyl bonded through an oxygen atom, which is bonded through a C_1-C_8 alkylenyl, wherein C_1-C_8 alkylenyl is as defined above. Illustrative examples of phenyl-O-(C_1-C_8 alkylenyl) include phenoxymethyl and 2-phenoxyethyl.

The term "Substituted phenyl-O-(C_1-C_8 alkylenyl)" means a phenyl-O-(C_1-C_8 alkylenyl) group, as defined above, that is substituted with from 1 to 4 substituents as defined above for R^2. Illustrative examples of substituted phenyl-O-(C_1-C_8 alkylenyl) include 4-fluorophenoxymethyl and 2-phenoxy-methylcarbonyl.

The term "Phenyl-S-(C_1-C_8 alkylenyl)" means a phenyl bonded through an sulfur atom, which is bonded through a C_1-C_8 alkylenyl, wherein C_1-C_8 alkylenyl is as defined above. Illustrative examples of phenyl-S-(C_1-C_8 alkylenyl) include thiophenoxymethyl and 2-thiophenoxyethyl.

The term "Substituted phenyl-S-(C_1-C_8 alkylenyl)" means a phenyl-S-(C_1-C_8 alkylenyl) group, as defined above, that is substituted with from 1 to 4 substituents as defined above for R^2. Illustrative examples of substituted phenyl-S-(C_1-C_8 alkylenyl) include 4-fluorothiophenoxymethyl and 2-thiophenoxy-methylcarbonyl.

The term "Phenyl-S(O)-(C_1-C_8 alkylenyl)" means a phenyl bonded through an sulfur atom, which is bonded through a C_1-C_8 alkylenyl, wherein C_1-C_8 alkylenyl is as defined above and the sulfur atom is also bonded to an oxygen atom. Illustrative examples of phenyl-S(O)-(C_1-C_8 alkylenyl) include phenyl-S(=O)-CH_2 and phenyl-S(=O)-CH_2CH_2.

The term "Substituted phenyl-S(O)-(C_1-C_8 alkylenyl)" means a phenyl-S(O)-(C_1-C_8 alkylenyl) group, as defined above, that is substituted with from 1 to 4 substituents as defined above for R^2. Illustrative examples of substituted phenyl-S(O)-(C_1-C_8 alkylenyl) include (4-Fluoro-phenyl)-S(=O)-CH_2 and phenyl-S(=O)-$CH_2C(=O)$.

The term "Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl)" means a phenyl bonded through an sulfur atom, which is bonded through a C_1-C_8 alkylenyl, wherein C_1-C_8 alkylenyl is as defined above and the sulfur atom is also bonded to two oxygen atoms. Illustrative examples of phenyl-$S(O)_2$-(C_1-C_8 alkylenyl) include phenyl-$S(=O)_2$-CH_2 and phenyl-$S(=O)_2$-CH_2CH_2.

The term "Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl)" means a phenyl-$S(O)_2$-(C_1-C_8 alkylenyl) group, as defined above, that is substituted with from 1 to 4 substituents as defined above for R^2. Illustrative examples of substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl) include (4-Fluoro-phenyl)-$S(=O)_2$-CH_2 and phenyl-$S(=O)_2$-$CH_2C(=O)$.

The term "(C_1-C_6 alkyl)-$S(O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a sulfur atom, which is bonded through a nitrogen atom, which is bonded through a carbon atom, wherein the sulfur atom is bonded to two oxygen atoms, the nitrogen atom is bonded to a hydrogen atom, and the carbon atom is doubly bonded to an oxygen atom to form a carbonyl group; and when m is 1, the term means a C_1-C_6 alkyl group, as defined above, bonded through a sulfur atom, which is bonded through a nitrogen atom, which is bonded through a carbon atom, which is bonded through a C_1-C_8 alkylenyl group, as defined above, wherein the sulfur atom is bonded to two oxygen atoms, the nitrogen atom is bonded to a hydrogen atom, and the carbon atom is doubly bonded to an oxygen atom to form a carbonyl group. Illustrative examples of (C_1-C_6 alkyl)-$S(=O)_2$-N(H)-C(O)-(C_1-C_8 alkylenyl)$_m$ include CH_3-$S(O)_2$-N(H)-C(=O) and CH_3-$S(O)_2$-N(H)-C(=O)-CH_2.

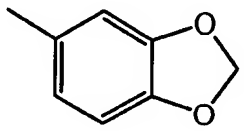
The term "(C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$", wherein m is an integer of 0 or 1, means, when m is 0, a C_1-C_6 alkyl group, as defined above, bonded through a carbon atom, which is bonded through a nitrogen atom, which is bonded through a sulfur atom, wherein the sulfur atom is bonded to two oxygen atoms, the nitrogen atom is bonded to a hydrogen atom, and the carbon atom is doubly bonded to an oxygen atom to form a carbonyl group; and when m is 1, the term means a C_1-C_6 alkyl group, as defined above, bonded through a carbon atom, which is bonded through a nitrogen atom, which is bonded through a sulfur atom, which is bonded through a C_1-C_8 alkylenyl group, as defined above, wherein the sulfur atom is bonded to two oxygen atoms, the nitrogen atom is bonded to a hydrogen atom, and the carbon atom is doubly bonded to an oxygen atom to form a carbonyl group. Illustrative examples of (C_1-C_6 alkyl)-C(O)-N(H)-$S(O)_2$-(C_1-C_8 alkylenyl)$_m$ include CH_3-C(=O)-N(H)-$S(=O)_2$ and CH_3-C(=O)-N(H)-$S(=O)_2$-CH_2.

Preferred substituents for substituted phenyl, substituted naphthyl (i.e., substituted 1-naphthyl or substituted 2-naphthyl), and preferred substituents at

carbon atoms for substituted 5-membered, monocyclic heteroaryl, substituted 6-membered, monocyclic heteroaryl, and substituted 9- or 10-membered, fused-bicyclic heteroaryl are C_1-C_4 alkyl, halo, OH, O-C_1-C_4 alkyl, 1,2-methylenedioxy, oxo ("=O"), CN, NO_2, N_3, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $C(O)CH_3$, $OC(O)$-C_1-C_4 alkyl, C(O)-H, CO_2H, CO_2-(C_1-C_4 alkyl), C(O)-N(H)OH, $C(O)NH_2$, C(O)NHMe, $C(O)N(Me)_2$, $NHC(O)CH_3$, $N(H)C(O)NH_2$, SH, S-C_1-C_4 alkyl, C≡CH, C(=NOH)-H, $C(=NOH)$-CH_3, CH_2OH, CH_2NH_2, $CH_2N(H)CH_3$, $CH_2N(CH_3)_2$, C(H)F-OH, CF_2-OH, $S(O)_2NH_2$, $S(O)_2N(H)CH_3$, $S(O)_2N(CH_3)_2$, S(O)-CH_3, $S(O)_2CH_3$, $S(O)_2CF_3$, or $NHS(O)_2CH_3$.

Especially preferred substituents are 1,2-methylenedioxy, methoxy, ethoxy, -O-$C(O)CH_3$, carboxy, carbomethoxy, and carboethoxy.

The term "1,2-methylenedioxy" means the diradical group -O-CH_2-O-, wherein the substituent 1,2-methylenedioxy is bonded to adjacent carbon atoms of the group which is substituted to form a 5-membered ring. Illustrative examples of groups substituted by 1,2-methylenedioxy include 1,3-benzoxazol-5-yl of formula B



B

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which is a phenyl group substituted by 1,2-methylenedioxy.

A fused-bicyclic group is a group wherein two ring systems share two, and only two, atoms.

It should be appreciated that the groups heteroaryl or heterocycloalkyl may not contain two ring atoms bonded to each other which atoms are oxygen and/or sulfur atoms.

The term "oxo" means =O. Oxo is attached at a carbon atom unless otherwise noted. Oxo, together with the carbon atom to which it is attached forms a carbonyl group (i.e., C=O).

The term "heteroatom" includes O, S, S(O), $S(O)_2$, N, N(H), and N(C_1-C_6 alkyl).

The term "halo" includes fluoro, chloro, bromo, and iodo.

The term "amino" means NH_2.

The phrase "two adjacent, substantially sp^2 carbon atoms" means carbon atoms that comprise a carbon-carbon double bond that is capable of being substituted on each carbon atom, wherein the carbon-carbon double bond is contained in an aromatic or nonaromatic, cyclic or acyclic, or carbocyclic or heterocyclic group.

The phrase "tertiary organic amine" means a trisubstituted nitrogen group wherein the 3 substituents are independently selected from C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl, or wherein two of the substituents are taken together with the nitrogen atom to which they are bonded to form a 5- or 6-membered, monocyclic heterocycle containing one nitrogen atom and carbon atoms, and the third substituent is selected from C_1-C_{12} alkyl and benzyl, or wherein the three substituents are taken together with the nitrogen atom to which they are bonded to form a 7- to 12-membered bicyclic heterocycle containing 1 or 2 nitrogen atoms and carbon atoms, and optionally a C=N double bond when 2 nitrogen atoms are present. Illustrative examples of tertiary organic amine include triethylamine, diisopropylethylamine, benzyl diethylamino, dicyclohexylmethyl-amine, 1,8-diazabicycle[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (TED), and 1,5-diazabicycle[4.3.0]non-5-ene.

The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

The term "admixed" and the phrase "in admixture" are synonymous and mean in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

The term "patient" means a mammal. Preferred patients are humans, cats, dogs, cows, horses, pigs, and sheep.

The term "animal" means a mammal, as defined above. Preferred animals include humans, cats, dogs, horses, pigs, sheep, cows, monkeys, rats, mice, guinea pigs, and rabbits.

The term "mammal" includes humans, companion animals such as cats and dogs, primates such as monkeys and chimpanzees, and livestock animals such as horses, cows, pigs, and sheep.

The phrase "livestock animals" as used herein refers to domesticated quadrupeds, which includes those being raised for meat and various byproducts, e.g., a bovine animal including cattle and other members of the genus Bos, a porcine animal including domestic swine and other members of the genus Sus, an ovine animal including sheep and other members of the genus Ovis, domestic goats and other members of the genus Capra; domesticated quadrupeds being raised for specialized tasks such as use as a beast of burden, e.g., an equine animal including domestic horses and other members of the family Equidae, genus Equus, or for searching and sentinel duty, e.g., a canine animal including domestic dogs and other members of the genus Canis; and domesticated quadrupeds being raised primarily for recreational purposes, e.g., members of Equus and Canis, as well as a feline animal including domestic cats and other members of the family Felidae, genus Felis.

The phrase "anticancer effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit, halt, or cause regression of the cancer being treated in a particular patient or patient population. For example in humans or other mammals, an anticancer effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular cancer and patient being treated.

The phrase "anti-arthritic effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit, halt, or cause regression of the arthritis being treated in a particular patient or patient population. For example in humans or other mammals, an anti-arthritic effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular arthritis and patient being treated.

The phrase "MMP-13 inhibiting amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, sufficient to inhibit an enzyme matrix metalloproteinase-13, including a truncated form thereof, including a catalytic domain thereof, in a particular animal or animal

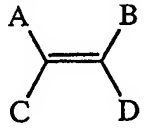
population. For example in a human or other mammal, an MMP-13 inhibiting amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular MMP-13 enzyme and patient being treated.

It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration, is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

The phrases "effective amount" and "therapeutically effective amount" are synonymous and mean an amount of a compound of the present invention, a pharmaceutically acceptable salt thereof, or a solvate thereof, sufficient to effect an improvement of the condition being treated when administered to a patient suffering from a disease that is mediated by MMP-13 and optionally from 0 to 12 additional MMP enzymes.

The term "tautomer" means a form of invention compound existing in a state of equilibrium with an isomeric form of the invention compound, wherein the invention compound is able to react according to either form by virtue of the ability of the forms to interconvert by isomerization in situ, including in a reaction mixture, in an in vitro biological assay, or in vivo.

The term "(*E*)" means entgegen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher ranking substituent groups, as determined according to the Cahn-Ingold-Prelog ranking system, on opposite sides of the double bond. An (*E*) double bond is illustrated below by the compound of Formula (W)

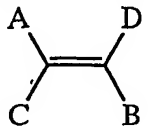


(W)

, wherein the two higher-ranking substituents are groups A and D.

The term "(*Z*)" means zusammen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher ranking substituent groups, as determined according to the Cahn-Ingold-

Prelog ranking system, on the same side of the double bond. A (Z) double bond is illustrated below by the compound of Formula (X)



(X)

, wherein the two higher-ranking substituents are groups A and D.

It should be appreciated that the S1' site of MMP-13 was previously thought to be a grossly linear channel which contained an opening at the top that allowed an amino acid side chain from a substrate molecule to enter during binding, and was closed at the bottom. Applicants has discovered that the S1' site is actually composed of an S1' channel angularly connected to a newly discovered pocket which applicant calls the S1" site. The S1" site is open to solvent at the bottom, which can expose a functional group of Applicants' invention compounds to solvent. For illustrative purposes, the S1' site of the MMP-13 enzyme can now be thought of as being like a sock with a hole in the toes, wherein the S1' channel is the region from approximately the opening to the ankle, and the S1" site is the foot region below the ankle, which foot region is angularly connected to the ankle region.

More particularly, the S1' channel is a specific part of the S1' site and is formed largely by Leu218, Val219, His222 and by residues from Leu239 to Tyr244. The S1" binding site which has been newly discovered is defined by residues from Tyr246 to Pro255. The S1" site contains at least two hydrogen bond donors and aromatic groups which interact with an invention compound.

Without wishing to be bound by any particular theory, the inventors believe that the S1" site could be a recognition site for triple helix collagen, the natural substrate for MMP-13. It is possible that the conformation of the S1" site is modified only when an appropriate compound binds to MMP-13, thereby interfering with the collagen recognition process. This newly discovered pattern of binding offers the possibility of greater selectivity than what is achievable with the binding pattern of known selective inhibitors of MMP-13, wherein the known binding pattern requires ligation of the catalytic zinc atom at the active site and occupation the S1' channel, but not the S1" site.

The term "Thr245" means threonine 245 of an MMP-13 enzyme.

The term "Thr247" means threonine 247 of an MMP-13 enzyme.

The term "Met253" means methionine 253 of an MMP-13 enzyme.

The term "His251" means histidine 251 of an MMP-13 enzyme.

It should be appreciated that the matrix metalloproteinases include, but are not limited to, the following enzymes:

MMP-1, also known as interstitial collagenase, collagenase-1, or fibroblast-type collagenase;

MMP-2, also known as gelatinase A or 72 kDa Type IV collagenase;

MMP-3, also known as stromelysin or stromelysin-1;

MMP-7, also known as matrilysin or PUMP-1;

MMP-8, also known as collagenase-2, neutrophil collagenase or polymorphonuclear-type ("PMN-type") collagenase;

MMP-9, also known as gelatinase B or 92 kDa Type IV collagenase;

MMP-10, also known as stromelysin-2;

MMP-11, also known as stromelysin-3;

MMP-12, also known as metalloelastase;

MMP-13, also known as collagenase-3;

MMP-14, also known as membrane-type ("MT") 1-MMP or MT1-MMP;

MMP-15, also known as MT2-MMP;

MMP-16, also known as MT3-MMP;

MMP-17, also known as MT4-MMP;

MMP-18; and

MMP-19.

Other known MMPs include MMP-26 (Matrilysin-2).

For the purposes of this invention, the term "arthritis", which is synonymous with the phrase "arthritic condition", includes osteoarthritis, rheumatoid arthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, and psoriatic arthritis. An allosteric inhibitor of MMP-13 having an anti-arthritic effect is a compound as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the arthritic diseases and disorders listed above.

The term "IC_{50}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to inhibit an enzyme's catalytic activity by 50%.

The term "ED_{40}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in about 40% of a patient group.

The term "ED_{30}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in 30% of a patient group.

The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

The term "admixed" and the phrase "in admixture" are synonymous and mean in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

As used herein, the phrase "cartilage damage" means a disorder of hyaline cartilage and subchondral bone characterized by hypertrophy of tissues in and around the involved joints, which may or may not be accompanied by deterioration of hyaline cartilage surface.

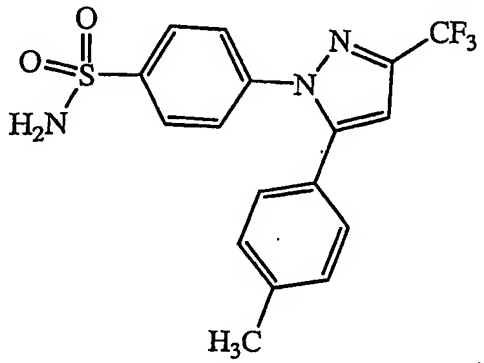
The phrase "treating", which is related to the terms "treat" and "treated", means administration of an invention combination as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the diseases and disorders listed above.

The phrase "invention compound" means a compound of Formula I, or a pharmaceutically acceptable salt thereof, as fully defined above.

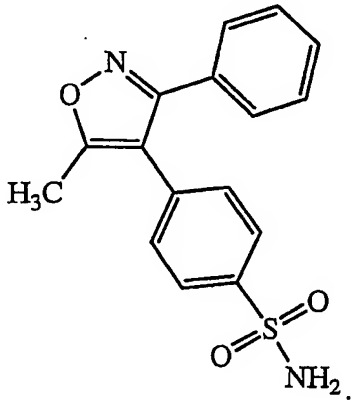
The term "nontoxic" means the efficacious dose is 10 times or greater than the dose at which a toxic effect is observed in 10% or more of a patient population.

The term "celecoxib" means the compound named 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-benzenesulfonamide. Celecoxib is a selective cyclooxygenase-2 ("COX-2") inhibitor currently approved by the FDA for the treatment of osteoarthritis, rheumatoid arthritis, and Polyposis-familial adenomatus. Celecoxib is marketed under the tradename "Celebrex". Celecoxib is currently in clinical trials for the treatment of bladder cancer, chemopreventative-

lung cancer, and post-operative pain, and is registered for the treatment of dysmenorrhea. Celecoxib has the structure drawn below:



The term "valdecoxib" means the compound named 4-(5-methyl-3-phenyl-4-isoxazolyl)-benzenesulfonamide. Valdecoxib is a selective COX-2 inhibitor that has been approved by the FDA for treating osteoarthritis, rheumatoid arthritis, dysmenorrhea, and general pain, and is marketed under the tradename "Bextra". Valdecoxib is in clinical trials for the treatment of migraine. Valdecoxib has the structure drawn below:



It should be appreciated that COX-2 is also known as prostaglandin synthase-2 and prostaglandin PGH_2 synthase.

A selective inhibitor of COX-2 means compounds that inhibit COX-2 selectively versus COX-1 such that a ratio of IC_{50} for a compound with COX-1 divided by a ratio of IC_{50} for the compound with COX-2 is greater than, or equal to, 5, where the ratios are determined in one or more assays. All that is required to determine whether a compound is a selective COX-2 inhibitor is to assay a compound in one of a number of well know assays in the art.

The term "NSAID" is an acronym for the phrase "nonsteroidal anti-inflammatory drug", which means any compound which inhibits cyclooxygenase-1 ("COX-1") and cyclooxygenase-2. Most NSAIDs fall within one of the following five structural classes: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and sulindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, peroxicam, sudoxicam, and isoxicam. Other useful NSAIDs include aspirin, acetominophen, indomethacin, and phenylbutazone. Selective inhibitors of cyclooxygenase-2 as described above may be considered to be NSAIDs also.

The term "drugs", which is synonymous with the phrases "active components", "active compounds", and "active ingredients", includes celecoxib, or a pharmaceutically acceptable salt thereof, valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, and may further include one or two of the other therapeutic agents described above.

It should be appreciated that in the Summary of the Invention above, the term "Embodiment" refers to an aspect of this invention. The Embodiments in the Summary of the Invention are numbered for ease of referral.

The compounds of Formula I, or pharmaceutically acceptable salts thereof, or tautomers thereof, include compounds which are invention compounds. An allosteric inhibitor of MMP-13 is any compound of Formula I that binds allosterically into the S1' site of the MMP-13 enzyme, including the S1' channel, and a newly discovered S1" site, without ligating, coordinating, or binding the catalytic zinc of the MMP-13.

An invention compound that is an allosteric inhibitor of MMP-13 may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying an alkyne test compound for inhibition of MMP-13 as described below in Biological Methods 1 or 2, and for allosteric inhibition of MMP-13 by assaying the test invention compound for inhibition of MMP-13 in the presence of an inhibitor to the catalytic zinc of MMP-13 as described below in Biological Methods 3 or 4.

Further, an invention compound having an anti-inflammatory, an analgesic, anti-arthritic, or a cartilage damage inhibiting effect, or any combination of these effects, may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying the invention compound in any number of well known assays for measuring determining the invention compound's effects on cartilage damage, arthritis, inflammation, or pain. These assays include in vitro assays that utilize cartilage samples and in vivo assays in whole animals that measure cartilage degradation, inhibition of inflammation, or pain alleviation.

For example with regard to assaying cartilage damage in vitro, an amount of an invention compound or control vehicle may be administered with a cartilage damaging agent to cartilage, and the cartilage damage inhibiting effects in both tests studied by gross examination or histopathologic examination of the cartilage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content. Further, in vivo assays to assay cartilage damage may be performed as follows: an amount of an invention compound or control vehicle may be administered with a cartilage damaging agent to an animal, and the effects of the invention compound being assayed on cartilage in the animal may be evaluated by gross examination or histopathologic examination of the cartilage, by observation of the effects in an acute model on functional limitations of the affected joint that result from cartilage damage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content.

Several methods of identifying an invention compound with cartilage damage inhibiting properties are described below. The amount to be administered in an assay is dependent upon the particular assay employed, but in any event is not higher than the well known maximum amount of a compound that the particular assay can effectively accommodate.

Similarly, invention compounds having pain-alleviating properties may be identified using any one of a number of in vivo animal models of pain.

Still similarly, invention compounds having anti-inflammatory properties may be identified using any one of a number of in vivo animal models of

inflammation. For example, for an example of inflammation models, see United States patent number 6, 329,429, which is incorporated herein by reference.

Still similarly, invention compounds having anti-arthritic properties may be identified using any one of a number of in vivo animal models of arthritis. For example, for an example of arthritis models, see also United States patent number 6, 329,429.

Other mammalian diseases and disorders which are treatable by administration of an invention combination alone, or contained in a pharmaceutical composition as defined below, include: fever (including rheumatic fever and fever associated with influenza and other viral infections), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic

retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock), epilepsy, convulsions, and septic shock.

Other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are ≥10, ≥20, ≥50, ≥100, or ≥1000 times more potent versus MMP-13 than versus at least two of any other MMP enzyme or TACE.

Still other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are selective inhibitors of MMP-13 versus 2, 3, 4, 5, 6, or 7 other MMP enzymes, or versus TACE and 1, 2, 3, 4, 5, 6, or 7 other MMP enzymes.

It should be appreciated that selectivity of a compound of Formula I, or a pharmaceutically acceptable salt thereof, is a multidimensional characteristic that includes the number of other MMP enzymes and TACE over which selectivity for MMP-13 inhibition is present and the degree of selectivity of inhibition of MMP-13 over another particular MMP or TACE, as measured by, for example, the IC_{50} in micromolar concentration of the compound for the inhibition of the other MMP enzyme or TACE divided by the IC_{50} in micromolar concentration of the compound for the inhibition of MMP-13.

As discussed above, one aspect of the present invention is novel compounds that are selective inhibitors of the enzyme MMP-13. A selective inhibitor of MMP-13, as used in the present invention, is a compound that is ≥5X more potent *in vitro* versus MMP-13 than versus at least one other matrix metalloproteinase enzyme such as, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, or MMP-14, or versus tumor necrosis factor alpha convertase ("TACE"). A preferred aspect of the present invention is novel compounds that are selective inhibitors of MMP-13 versus MMP-1.

The invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, which has an IC_{50} with any MMP enzyme that is less than or equal to 50 micromolar. Preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that is less than or equal to 50 micromolar. More preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that is less than or equal to 10 micromolar.

Examples of biological methods useful for determining IC_{50}s for the invention compounds with an MMP are described below in Biological Methods 1 to 4. Any compound of Formula I, or a pharmaceutically acceptable salt thereof, or any form thereof as defined above, that does not have an IC_{50} with any MMP enzyme that is less than, or equal to, 10 micromolar is excluded from this invention.

Some of the invention compounds are capable of further forming nontoxic pharmaceutically acceptable salts, including, but not limited to, acid addition and/or base salts. The acid addition salts are formed from basic invention compounds, whereas the base addition salts are formed from acidic invention compounds. All of these forms are within the scope of the compounds useful in the invention.

Pharmaceutically acceptable acid addition salts of the basic invention compounds include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate,

methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," J. of Pharma. Sci., 1977;66:1).

An acid addition salt of a basic invention compound is prepared by contacting the free base form of the compound with a sufficient amount of a desired acid to produce a nontoxic salt in the conventional manner. The free base form of the compound may be regenerated by contacting the acid addition salt so formed with a base, and isolating the free base form of the compound in the conventional manner. The free base forms of compounds prepared according to a process of the present invention differ from their respective acid addition salt forms somewhat in certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise free base forms of the invention compounds and their respective acid addition salt forms are equivalent for purposes of the present invention.

A nontoxic pharmaceutically acceptable base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a metal cation such as an alkali or alkaline earth metal cation, or an amine, especially an organic amine. Examples of suitable metal cations include sodium cation (Na^+), potassium cation (K^+), magnesium cation (Mg^{2+}), calcium cation (Ca^{2+}), and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

A base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a sufficient amount of a desired base to produce the salt in the conventional manner. The free acid form of the compound may be regenerated by contacting the salt form so formed with an acid, and isolating the free acid of the compound in the conventional manner. The free acid forms of the invention compounds differ from their respective salt forms somewhat in certain physical properties such as solubility, crystal structure,

hygroscopicity, and the like, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain invention compounds can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

Certain of the invention compounds possess one or more chiral centers, and each center may exist in the R or S configuration. An invention compound includes any diastereomeric, enantiomeric, or epimeric form of the compound, as well as mixtures thereof.

Additionally, certain invention compounds may exist as geometric isomers such as the entgegen (E) and zusammen (Z) isomers of 1,2-disubstituted alkenyl groups or cis and trans isomers of disubstituted cyclic groups. An invention compound includes any cis, trans, syn, anti, entgegen (E), or zusammen (Z) isomer of the compound, as well as mixtures thereof.

Certain invention compounds can exist as two or more tautomeric forms. Tautomeric forms of the invention compounds may interchange, for example, via enolization/de-enolization, 1,2-hydride, 1,3-hydride, or 1,4-hydride shifts, and the like. An invention compound includes any tautomeric form of the compound, as well as mixtures thereof.

Some compounds of the present invention have alkenyl groups, which may exist as entgegen or zusammen conformations, in which case all geometric forms thereof, both entgegen and zusammen, *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

Some compounds of the present invention have cycloalkyl groups, which may be substituted at more than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

The invention compounds also include isotopically-labelled compounds, which are identical to those recited above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that

can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of those described above in this invention can generally be prepared by carrying out the procedures incorporated by reference above or disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

All of the above-describe forms of an invention compound are included by the phrase "invention compound", a "compound of Formula I", a "compound of Formula I, or a pharmaceutically acceptable salt thereof", or any named species thereof, unless specifically excluded therefrom.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as etoricoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

This invention also relates to a method of or a pharmaceutical composition for treating inflammatory processes and diseases comprising administering a compound of this invention to a mammal, including a human, cat, livestock or dog, wherein said inflammatory processes and diseases are defined as above and said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

A.) where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal and/or antiviral therapeutic agents;

B.) where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

(1) NSAIDs;

(2) H_1 -receptor antagonists;

(3) kinin-B_1 - and B_2 -receptor antagonists;

(4) prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2 - and PGE-receptor antagonists;

(5) thromboxane A_2 (TXA_2-) inhibitors;

(6) 5-, 12- and 15-lipoxygenase inhibitors;

(7) leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 -inhibitors;

(8) PAF-receptor antagonists;

(9) gold in the form of an aurothio group together with one or more hydrophilic groups;

(10) immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine and methotrexate;

(11) anti-inflammatory glucocorticoids;

(12) penicillamine;

(13) hydroxychloroquine;

(14) anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone and benzbromarone;

C. where older mammals are being treated for disease conditions, syndromes and symptoms found in geriatric mammals, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting essentially of:

(1) cognitive therapeutics to counteract memory loss and impairment;

(2) anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

(3) antineoplastic agents selected from:

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine and

[2] vincristine;

(4) growth hormone secretagogues;

(5) strong analgesics;

(6) local and systemic anesthetics; and

(7) H_2 -receptor antagonists, proton pump inhibitors and other gastroprotective agents.

The active ingredient of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leucotriene receptor antagonists, IL-1 processing and release inhibitors, ILra, H_1 -receptor antagonists; kinin-B_1 - and B_2 -receptor antagonists; prostaglandin inhibitors such as PGD-, PGF- PGI_2 - and PGE-receptor antagonists; thromboxane A_2 (TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 - inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol and uricosuric agents, e.g., probenecid, sulfinpyrazone and benzbromarone.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure and myocardial infarction, selected from

vasodilators such as hydralazine, β-adrenergic receptor antagonists such as propranolol, calcium channel blockers such as nifedipine, α_2-adrenergic agonists such as clonidine, α-adrenergic receptor antagonists such as prazosin and HMG-CoA-reductase inhibitors (anti-hypercholesterolemics) such as lovastatin or atorvastatin.

The compounds of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, lasofoxifene, droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

The present invention also relates to the formulation of a compound of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in the feed composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the patient being

treated, even though the individual drugs making up said combination are not being administered to said patient simultaneously.

The invention method is useful in human and veterinary medicines for treating mammals suffering from one or more of the above-listed diseases and disorders.

All that is required to practice a method of this invention is to administer a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount that is therapeutically effective for preventing, inhibiting, or reversing the condition being treated. The invention compound can be administered directly or in a pharmaceutical composition as described below.

A therapeutically effective amount, or, simply, effective amount, of an invention compound will generally be from about 1 to about 300 mg/kg of subject body weight of the compound of Formula I, or a pharmaceutically acceptable salt thereof. Typical doses will be from about 10 to about 5000 mg/day for an adult subject of normal weight for each component of the combination. In a clinical setting, regulatory agencies such as, for example, the Food and Drug Administration ("FDA") in the U.S. may require a particular therapeutically effective amount.

In determining what constitutes a nontoxic effective amount or a therapeutically effective amount of an invention compound for treating, preventing, or reversing one or more symptoms of any one of the diseases and disorders described above that are being treated according to the invention methods, a number of factors will generally be considered by the medical practitioner or veterinarian in view of the experience of the medical practitioner or veterinarian, including the Food and Drug Administration guidelines, or guidelines from an equivalent agency, published clinical studies, the subject's (e.g., mammal's) age, sex, weight and general condition, as well as the type and extent of the disease, disorder or condition being treated, and the use of other medications, if any, by the subject. As such, the administered dose may fall within the ranges or concentrations recited above, or may vary outside them, ie, either below or above those ranges, depending upon the requirements of the individual subject, the severity of the condition being treated, and the particular therapeutic formulation being employed. Determination of a proper dose for a particular

situation is within the skill of the medical or veterinary arts. Generally, treatment may be initiated using smaller dosages of the invention compound that are less than optimum for a particular subject. Thereafter, the dosage can be increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Pharmaceutical compositions, described briefly here and more fully below, of an invention combination may be produced by formulating the invention combination in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Alternatively, the invention compounds may be formulated separately.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations.

The compositions to be employed in the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents commonly employed to treat any of the above-listed diseases and disorders.

The percentage of the active ingredients of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a total concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in

which a much higher proportion of the active ingredients are present, for example, up to about 95%.

Preferred routes of administration of an invention compound are oral or parenteral. However, another route of administration may be preferred depending upon the condition being treated. For exampled, topical administration or administration by injection may be preferred for treating conditions localized to the skin or a joint. Administration by transdermal patch may be preferred where, for example, it is desirable to effect sustained dosing.

It should be appreciated that the different routes of administration may require different dosages. For example, a useful intravenous ("IV") dose is between 5 and 50 mg, and a useful oral dosage is between 20 and 800 mg, of a compound of Formula I, or a pharmaceutically acceptable salt thereof. The dosage is within the dosing range used in treatment of the above-listed diseases, or as would be determined by the needs of the patient as described by the physician.

The invention compounds may be administered in any form. Preferably, administration is in unit dosage form. A unit dosage form of the invention compound to be used in this invention may also comprise other compounds useful in the therapy of diseases described above. A further description of pharmaceutical formulations useful for administering the invention compounds and invention combinations is provided below.

The active components of the invention combinations, may be formulated together or separately and may be administered together or separately. The particular formulation and administration regimens used may be tailored to the particular patient and condition being treated by a practitioner of ordinary skill in the medical or pharmaceutical arts.

The advantages of using an invention compound in a method of the instant invention include the nontoxic nature of the compounds at and substantially above therapeutically effective doses, their ease of preparation, the fact that the compounds are well-tolerated, and the ease of topical, IV, or oral administration of the drugs.

Another important advantage is that the present invention compounds more effectively target a particular disease that is responsive to inhibition of MMP-13 with fewer undesirable side effects than similar compounds that inhibit

MMP-13 that are not invention compounds. This is so because the instant invention compounds of Formula I, or a pharmaceutically acceptable salt thereof, do not directly, or indirectly via a bridging water molecule, ligate, coordinate to, or bind to the catalytic zinc cation of MMP-13, but instead bind at a different location from where natural substrate binds to MMP-13. The binding requirements of an allosteric MMP-13 binding site are unique to MMP-13, and account for the specificity of the invention compounds for inhibiting MMP-13 over any other MMP enzyme. This binding mode has not been reported in the art. Indeed, prior art inhibitors of MMP-13 bind to the catalytic zinc cations of other MMP enzymes as well as to the catalytic zinc cation of MMP-13, and are consequently significantly less selective inhibitors of MMP-13 enzyme.

The invention compounds which are invention compounds, and pharmaceutically acceptable salts thereof, are thus therapeutically superior to other inhibitors of MMP-13, or even tumor necrosis factor-alpha converting enzyme ("TACE"), because of fewer undesirable side effects from inhibition of the other MMP enzymes or TACE. For example, virtually all prior art MMP inhibitors tested clinically to date have exhibited an undesirable side effect known as muscoloskeletal syndrome ("MSS"). MSS is associated with administering an inhibitor of multiple MMP enzymes or an inhibitor of a particular MMP enzyme such as MMP-1. MSS will be significantly reduced in type and severity by administering the invention compound instead of any prior art MMP-13 inhibitor, or a pharmaceutically acceptable salt thereof. The invention compounds are superior to similar compounds that interact with the catalytic zinc cation of the MMP-13 enzyme as discussed above, even if similar compounds show some selectivity for the MMP-13.

It is expected that nearly all, if not all, compounds of Formula I, or pharmaceutically acceptable salts thereof, are invention compounds.

This advantage of the instant compounds will also significantly increase the likelihood that agencies which regulate new drug approvals, such as the United States Food and Drug Administration, will approve the instant compounds versus a competing similar compound that does not allosterically bind to MMP-13 as discussed above even in the unlikely event that the two compounds behaved similarly in clinical trials. These regulatory agencies are increasingly aware that

clinical trials, which test drug in limited population groups, do not always uncover safety problems with a drug, and thus all other things being equal, the agencies will favor the drug with the lowest odds of producing undesirable side effects.

Another important advantage is that the disease modifying properties of the invention compounds provide patients suffering from cartilage damage, arthritis, preferably osteoarthritis, inflammation and/or pain with both relief of symptoms and prevention or inhibition of the underlying disease pathology such as cartilage degradation. There is no currently approved drug for disease modification of cartilage damage, including in osteoarthritis.

Any invention compound is readily available, either commercially, or by synthetic methodology, well known to those skilled in the art of organic chemistry. For specific syntheses, see the examples below and the preparations of invention compound outlined in the Schemes below.

Intermediates for the synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by one of ordinary skill in the art of organic chemistry by adapting various synthetic procedures incorporated by reference above or that are well-known in the art of organic chemistry. These synthetic procedures may be found in the literature in, for example, Reagents for Organic Synthesis, by Fieser and Fieser, John Wiley & Sons, Inc, New York, 2000; Comprehensive Organic Transformations, by Richard C. Larock, VCH Publishers, Inc, New York, 1989; the series Compendium of Organic Synthetic Methods,1989,by Wiley-Interscience; the text Advanced Organic Chemistry, 4th edition, by Jerry March, Wiley-Interscience, New York,1992; or the Handbook of Heterocyclic Chemistry by Alan R. Katritzky, Pergamon Press Ltd, London, 1985, to name a few. Alternatively, a skilled artisan may find methods useful for preparing the intermediates in the chemical literature by searching widely available databases such as, for example, those available from the Chemical Abstracts Service, Columbus, Ohio, or MDL Information Systems GmbH (formerly Beilstein Information Systems GmbH), Frankfurt, Germany.

Preparations of the invention compounds may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources

or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, The Aldrich Chemical Company, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, BACHEM, BACHEM A.G., Switzerland, or Lancaster Synthesis Ltd, United Kingdom.

Syntheses of some invention compounds may utilize starting materials, intermediates, or reaction products that contain a reactive functional group. During chemical reactions, a reactive functional group may be protected from reacting by a protecting group that renders the reactive functional group substantially inert to the reaction conditions employed. A protecting group is introduced onto a starting material prior to carrying out the reaction step for which a protecting group is needed. Once the protecting group is no longer needed, the protecting group can be removed. It is well within the ordinary skill in the art to introduce protecting groups during a synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and then later remove them. Procedures for introducing and removing protecting groups are known and referenced such as, for example, in Protective Groups in Organic Synthesis, 2nd ed., Greene T.W. and Wuts P.G., John Wiley & Sons, New York: New York, 1991, which is hereby incorporated by reference.

Thus, for example, protecting groups such as the following may be utilized to protect amino, hydroxyl, and other groups: carboxylic acyl groups such as, for example, formyl, acetyl, and trifluoroacetyl; alkoxycarbonyl groups such as, for example, ethoxycarbonyl, tert-butoxycarbonyl (BOC), β,β,β-trichloroethoxycarbonyl (TCEC), and β-iodoethoxycarbonyl; aralkyloxycarbonyl groups such as, for example, benzyloxycarbonyl (CBZ), para-methoxybenzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl (FMOC); trialkylsilyl groups such as, for example, trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBDMS); and other groups such as, for example, triphenylmethyl (trityl), tetrahydropyranyl, vinyloxycarbonyl, ortho-nitrophenylsulfenyl, diphenylphosphinyl, para-toluenesulfonyl (Ts), mesyl, trifluoromethanesulfonyl, and benzyl. Examples of procedures for removal of

protecting groups include hydrogenolysis of CBZ groups using, for example, hydrogen gas at 50 psi in the presence of a hydrogenation catalyst such as 10% palladium on carbon, acidolysis of BOC groups using, for example, hydrogen chloride in dichloromethane, trifluoroacetic acid (TFA) in dichloromethane, and the like, reaction of silyl groups with fluoride ions, and reductive cleavage of TCEC groups with zinc metal.

General syntheses of the compounds of Formula I are outlined below in Schemes 1, 2, 3a, 3b, 3c, 4a, 4b, 4c, 5a, and 5b.

Compounds of Formula I where Y^5, Y^6, and Y^8 are CH can be prepared utilizing the reaction conditions presented in Schemes 1 and 2. In Scheme 1, the nitrogen atom of the oxazine or thiazine heterocycle (1) can be alkylated with an appropriately substituted alkylating agent such as iodomethane in the presence of cesium carbonate in dimethylformamide ("DMF") or tetrahydrofuran ("THF"). The halide (2) can be converted to the corresponding ester (3) in methanol/tetrahydrofuran under an atmosphere of carbon monoxide and catalyzed by bis(triphenylphosphine)Pd(II) dichloride, requiring reaction temperatures as high as 100 °C. The oxazine or thiazine intermediate (3) undergo a condensation reaction with appropriately substituted aldehydes in refluxing acetic anhydride containing a suitable base such as triethylamine. The ester intermediate (4) may be coupled with a variety of amines using trimethylaluminum in dichloromethane to yield amide intermediate (5). The exocyclic double bond of (5) may be reduced to compound (6) in the presence of 10% palladium on carbon in methanolic tetrahydrofuran under an atmosphere of hydrogen.

In Scheme 2, similar reaction conditions could be used to convert the quinolinone starting material (7) to the corresponding amide (12). As described in Scheme 1, alkylation followed by carbonylation and coupling the resulting ester (9) with appropriately substituted amines should yield the amide intermediate (10). Deprotonation of (10) at –78 °C using lithium diisopropylamide ("LDA) in THF followed by aldehyde condensation provides the exocyclic olefin (11). Hydrogenation of the exocyclic double bond of (11) using conditions previously described in Scheme 1 allows isolation of quinolinone derivative (12).

The synthesis of compounds of Formula I wherein Y^5, Y^6, or Y^8 are either CH or N is presented in Schemes 3a, 3b, and 3c. In Scheme 3a, wherein $Y^8 = N$, the 2-chloro atom of compound (13) can be selectively displaced with alcohol or thiol (14) in the presence of a base such as triethylamine and a suitable solvent like acetone at reaction temperatures ranging between 0 °C and 25 °C. Reduction of the nitro functionality with tin/HCl initiates intramolecular cyclization to compound (15) on warming.

Similar reaction conditions can be used to prepare compounds of Formula I where Y^6 is N. Replacement of compound (13) with (16) in Scheme 3a and using the reaction conditions previously described for (13) should allow the isolation of either the oxazine or thiazine derivatives (17).

However, as shown in Scheme 3b the synthesis of oxazines and thiazines of Formula I where Y^5 is N, require separate starting materials. For the thiazine (21), the thiol (19) is coupled to the 3-position of (18) using a base such as sodium hydride in refluxing THF. Based catalyzed hydrolysis of (20) to the corresponding thiol followed by coupling with chloroacetic acid and cyclization in a suitable solvent such as THF to give thiazine (21).

In Scheme 3c, the oxazine (24) can be prepared from compound (22) using a similar strategy previously used for (21). Base catalyzed addition of (22) to chloroacetic acid followed by cyclization affords intermediate (22). Compound (22) can undergo halogenation using bromine in an aprotic solvent such as DMF to give compound (24).

The synthesis of naphthyridinone derivatives is presented in Schemes 4a, 4b, and 4c. In Scheme 4a, wherein $Y^6 = N$, ortho-directed metallation of (25) in the presence of n-butyl lithium and tetramethylethylenediamine ("TMEDA") in THF at –78 °C followed by electrophilic quench with N-formylmorpholine yields the aldehyde (26) derivative. Condensation of the aldehyde utilizing the Wittig reaction can allow isolation of the acrylate (27). Deprotection of the amine using trifluoroacetic acid ("TFA") followed by base catalyzed cyclization should provide heterocycle (28). Hydrogenation of the lactam double bond in the presence of palladium on carbon yields the tetrahydronaphthyridinone (29).

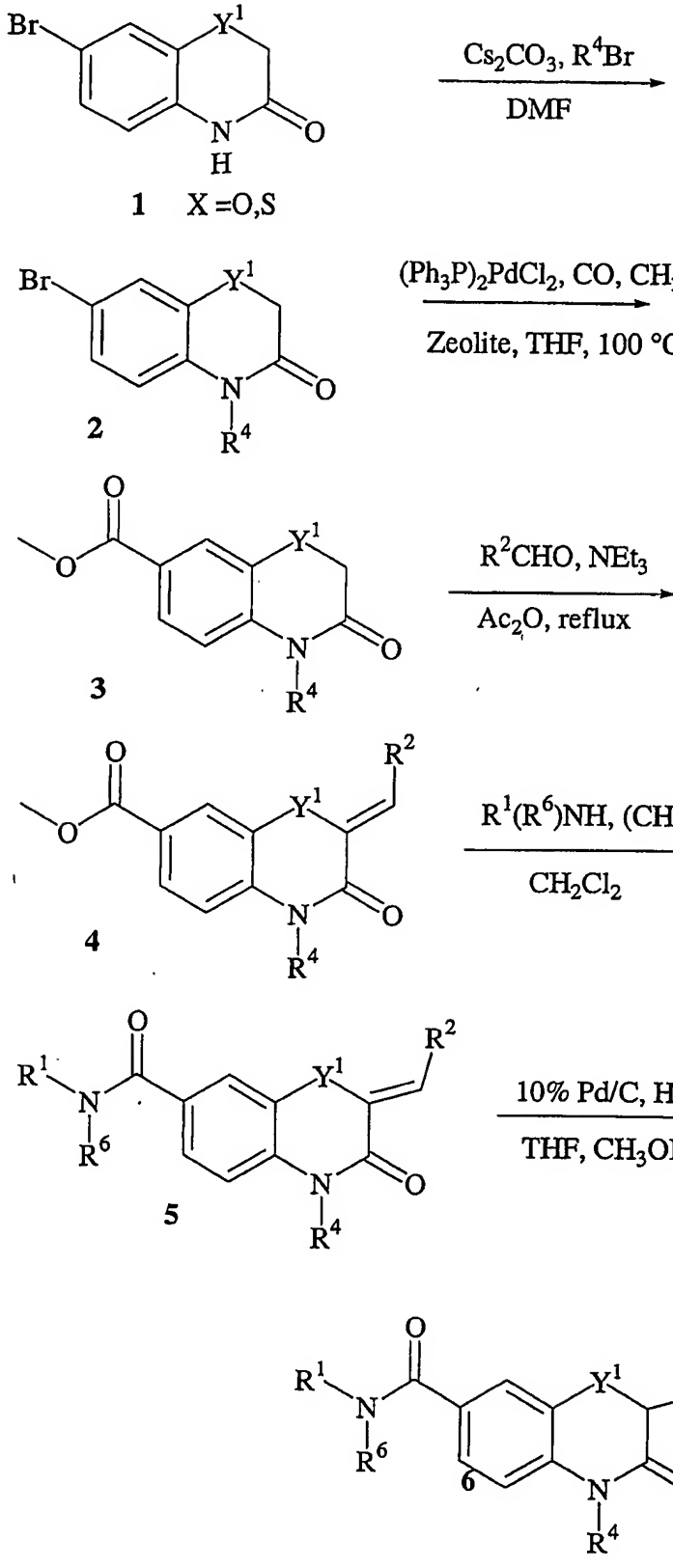
In Scheme 4b, wherein Y^5 = N, pyridine derivative (30) can be converted to the dihydronaphthyridinone (31) in one pot using palladium catalyzed coupling of methylacrylate with (30) in acetonitrile followed by base catalyzed cyclization to (31). Hydrogenation to the tetrahydro derivative (32) followed by nitration and subsequent reduction of the nitro functionality with Raney nickel in methanolic ammonia. Compound (33) can be diazotized and converted to the iodo derivative (34) in the presence of t-butylnitrite and copper(I)iodide in refluxing acetonitrile.

Similar reaction conditions are used for Y^8 = N as shown in Scheme 4c, methylacrylate coupling with compound (35) followed by base catalyzed cyclization and hydrogenation of the lactam double bond yields naphthyridinone (37).

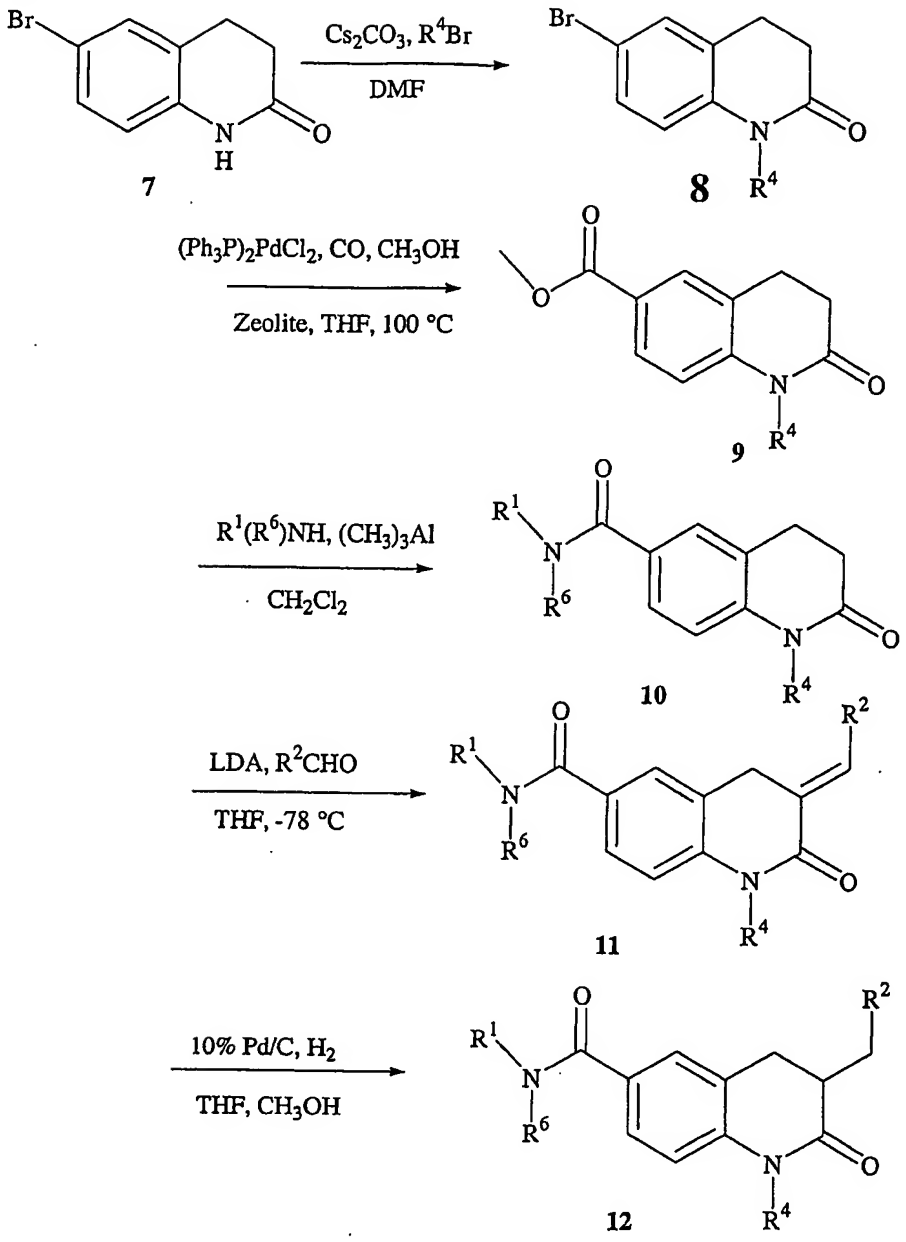
Compounds of Formula I wherein Q is a triple bond can be prepared as shown in Schemes 5a and 5b. In Scheme 5a, halogen containing analogs (38) can be converted directly to the corresponding alkynes in one step using appropriately substituted acetylenes in a base such as diisopropylethylamine with copper(I)iodide and bis(triphenylphosphine)palladium(II)dichloride as the catalyst in DMF with the reaction temperature ranging between 40 °C and 110 °C.

Alternatively in Scheme 5b, intermediates bearing a methoxy group in place of a halogen may be converted to the corresponding alcohol in the presence of BBr_3. The alcohol can be converted to the triflate (41) using triflic anhydride in pyridine. Using the same palladium catalyzed conditions previously described, triflate (41) can be converted to the corresponding alkyne derivatives.

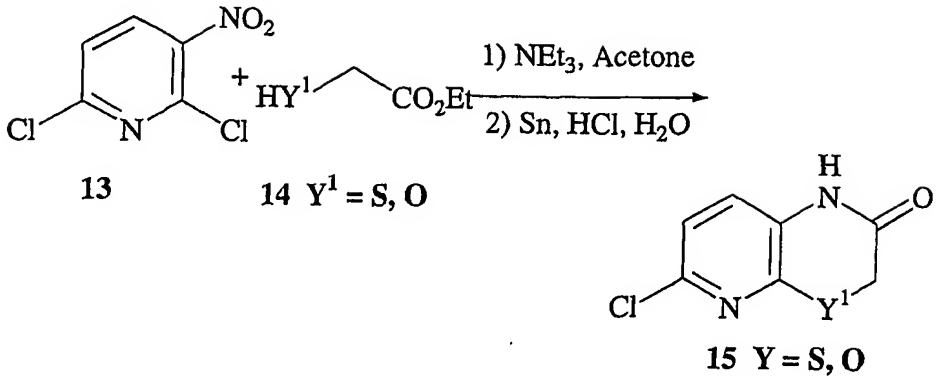
Scheme 1.


Br
Y1
N
H
O
1 X =O,S
Cs2CO3, R4Br
DMF
(Ph3P)2PdCl2, CO, CH3OH
Zeolite, THF, 100 °C
2
R4
3
R2CHO, NEt3
Ac2O, reflux
4
R2
R1(R6)NH, (CH3)3Al
CH2Cl2
5
R1
R6
10% Pd/C, H2
THF, CH3OH
6

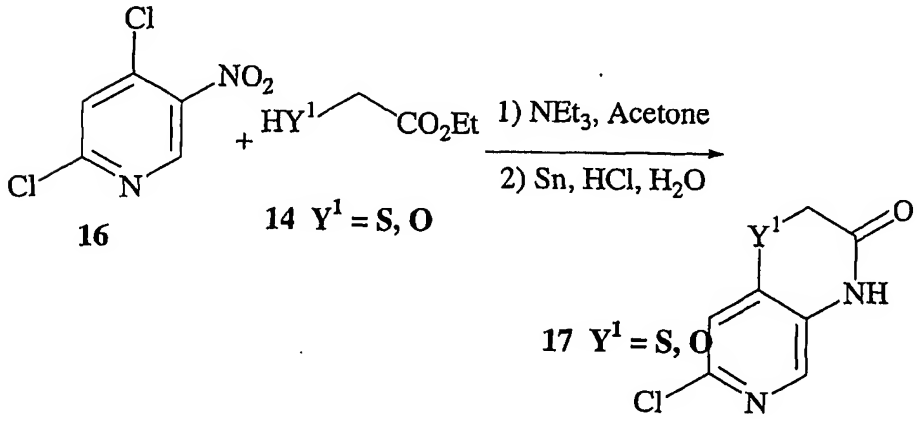
Scheme 2.


Br
Cs_2CO_3, R^4Br
DMF
N
H
O
7
8
R^4
$(Ph_3P)_2PdCl_2$, CO, CH_3OH
Zeolite, THF, 100 °C
9
$R^1(R^6)NH$, $(CH_3)_3Al$
CH_2Cl_2
10
LDA, R^2CHO
THF, -78 °C
11
10% Pd/C, H_2
THF, CH_3OH
12

Scheme 3a.

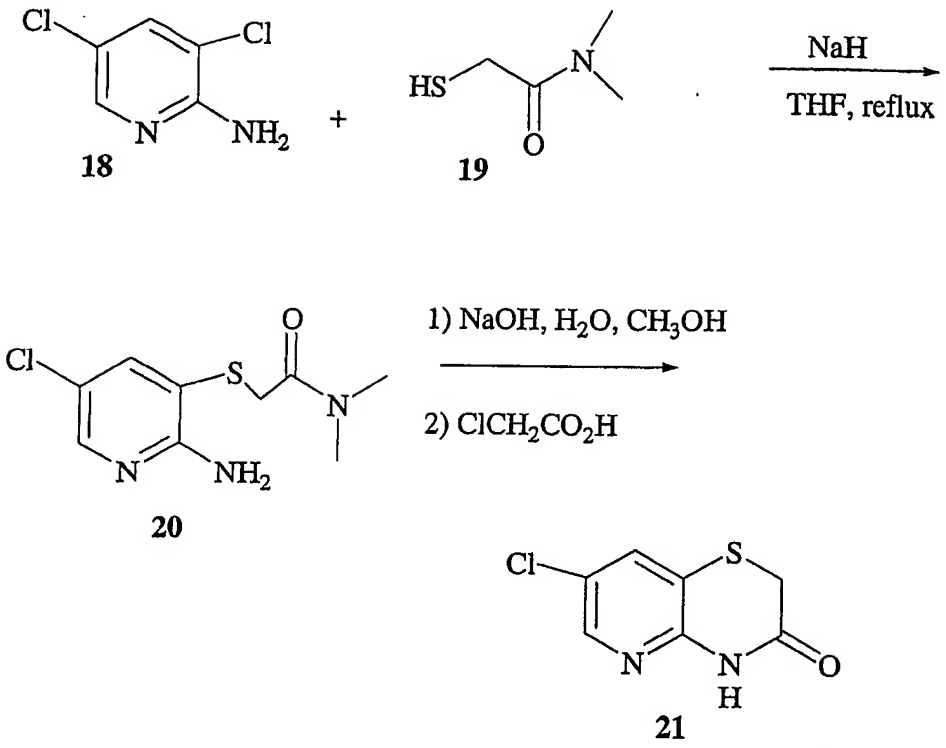


13 **14 Y^1 = S, O** **15 Y = S, O**

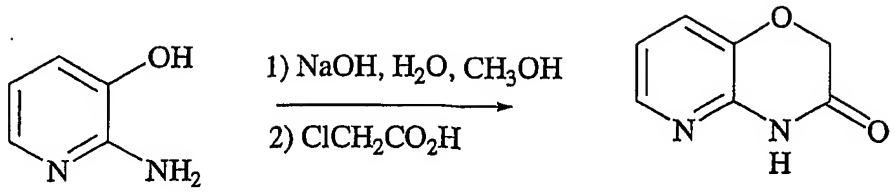


16 **14 Y^1 = S, O** **17 Y^1 = S, O**

Scheme 3b.

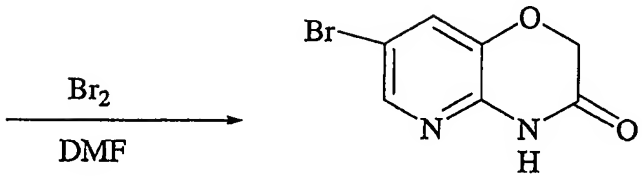

Cl
Cl
N
NH2
18
+
HS
N
O
19
NaH
THF, reflux
Cl
S
O
N
N
NH2
20
1) NaOH, H2O, CH3OH
2) ClCH2CO2H
Cl
S
N
N
H
O
21

Scheme 3c.



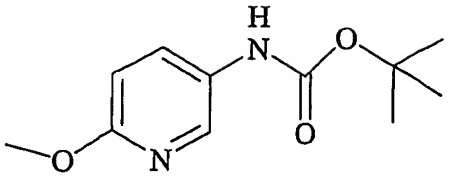
22

23



24

Scheme 4a.

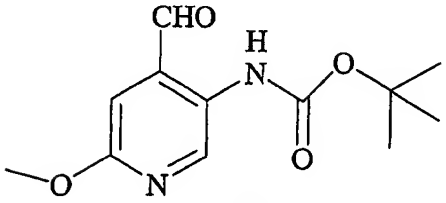


25

1) TMEDA, n-BuLi

THF, -78 °C

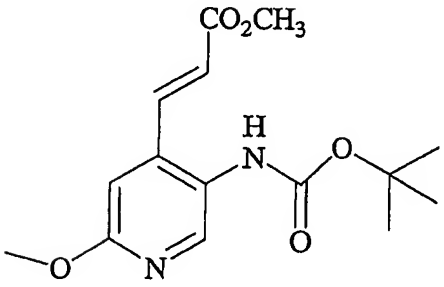
2) N-Formylmorpholine



26

$Ph_3PCH_2CO_2CH_3$

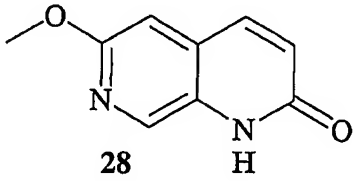
$NaOCH_3$, CH_3OH



27

1) TFA

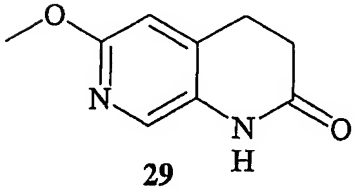
2) NaOH, CH_3OH



28

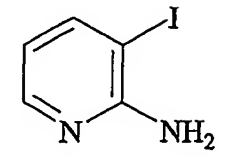
10% Pd/C, H_2

THF, AcOH



29

Scheme 4b.

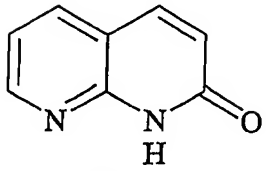


30

1) $CH=CHCO_2CH_3$, NEt_3

$Pd(AcO)_2$, CH_3CN

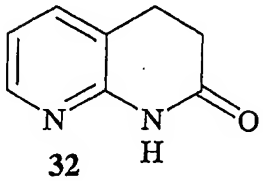
2) NaOH, CH_3OH/H_2O



31

10% Pd/C, H_2

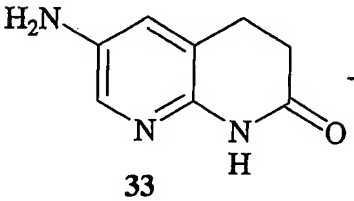
THF, AcOH



32

1) HNO_3, H_2SO_4

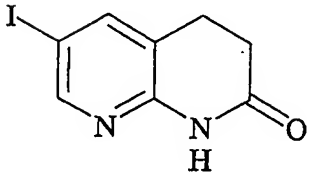
2) Raney Ni, NH_3/CH_3OH



33

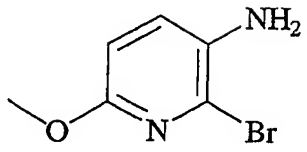
t-Butylnitrite, CuI

CH_3CN, reflux



34

Scheme 4c.

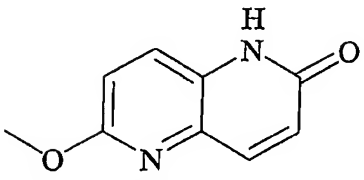


1) $CH=CHCO_2CH_3$, NEt_3

$Pd(AcO)_2$, CH_3CN

2) NaOH, CH_3OH/H_2O

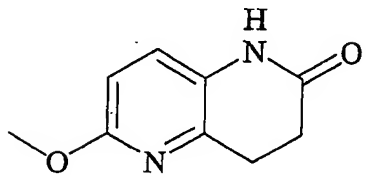
35



10% Pd/C, H_2

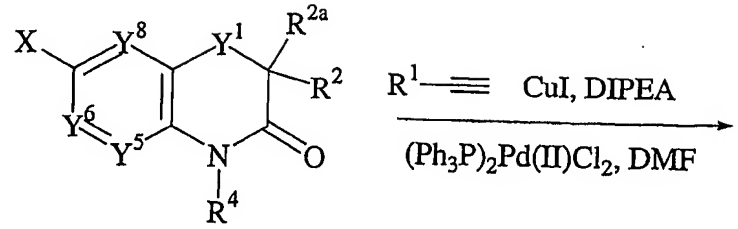
THF, AcOH

36

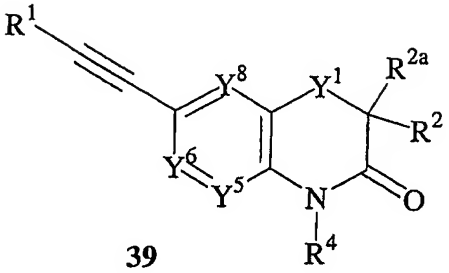


37

Scheme 5a.

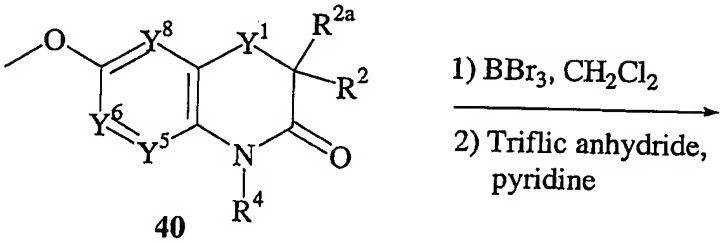


38 X = halo

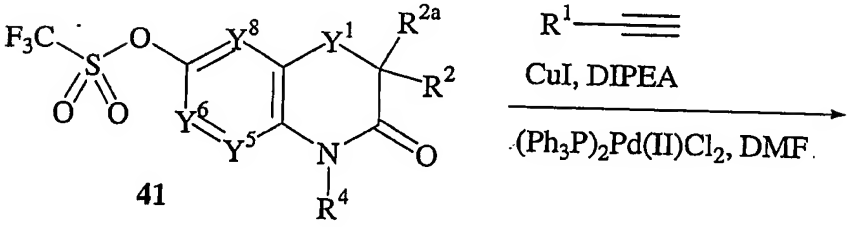


39

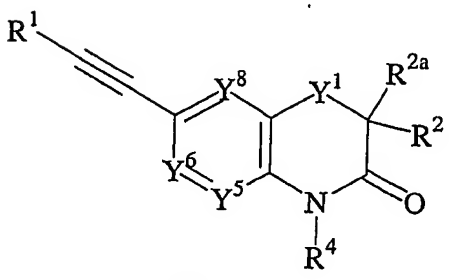
Scheme 5b.



40



41

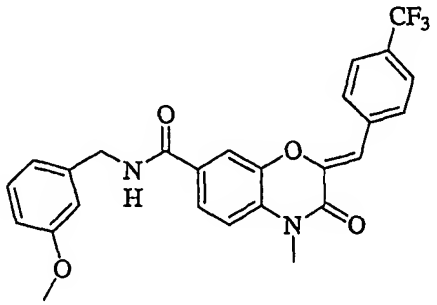


39

The following are examples that can be prepared using the reaction conditions described in Schemes 1and 2:

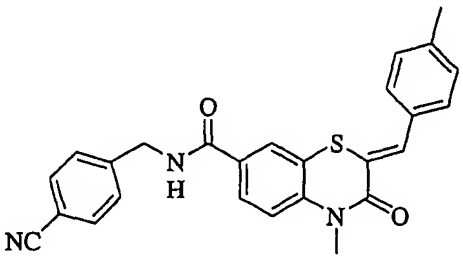
EXAMPLE 1

4-Methyl-3-oxo-2-(4-trifluoromethyl-benzylidene)-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 3-methoxy-benzylamide.



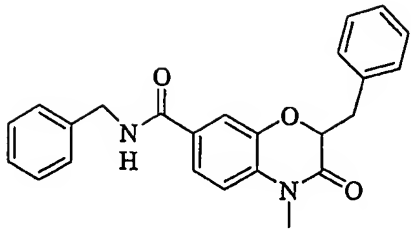
EXAMPLE 2

4-Methyl-2-(4-methyl-benzylidene)-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-cyano-benzylamide.



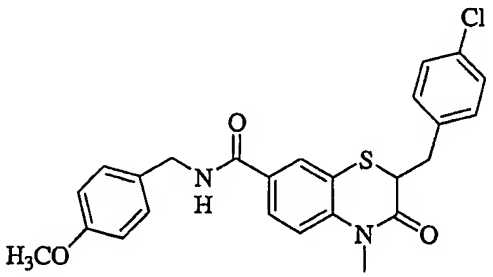
EXAMPLE 3

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid benzylamide.



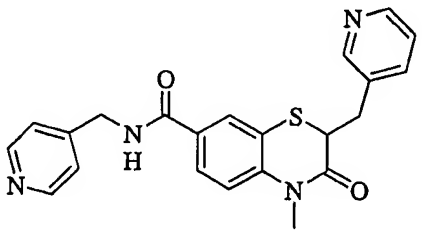
EXAMPLE 4

2-(4-Chloro-benzyl)-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazone-7-carboxylic acid-benzylamide.



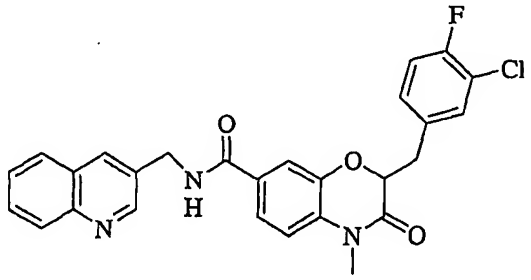
EXAMPLE 5

4-Methyl-3-oxo-2-pyridin-3-ylmethyl-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide.



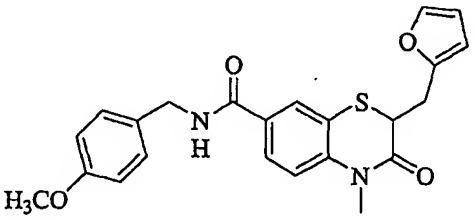
EXAMPLE 6

2-(3-Chloro-4-fluoro-benzyl)-4-methyl-3-oxo3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid (quinolin-3-ylmethyl)-amide.



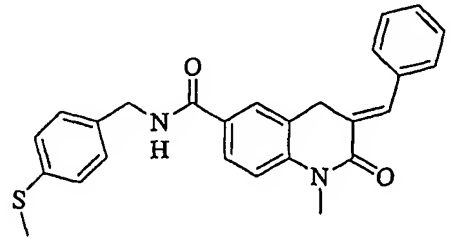
EXAMPLE 7

2-Furan-2-ylmethyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-methoxy-benzylamide.



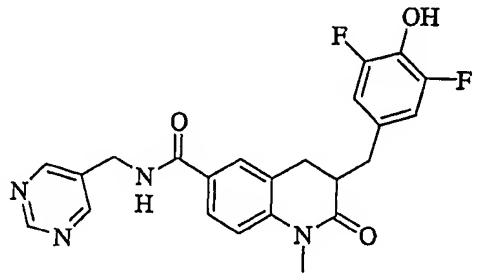
EXAMPLE 8

3-Benzylidene-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 4-methylsulfanyl-benzylamide.



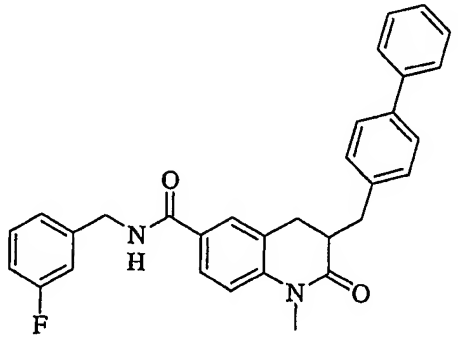
EXAMPLE 9

3-(3,5-Difluoro-4-hydroxy-benzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (pyrimidin-5-ylmethyl)-amide.



EXAMPLE 10

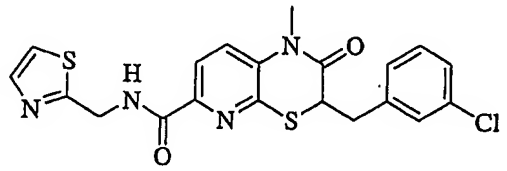
3-Biphenyl-4-ylmethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 3-fluoro-benzyl amide



Replacement of compound (1) in Scheme 1 with compounds (15), (17), (21), and (24) from Schemes 3a, 3b, and 3c, and using the reaction conditions previously described in Scheme 1, the following examples can be made:

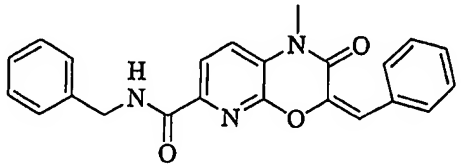
EXAMPLE 11

3-(3-Chloro-benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazine-6-carboxylic acid (thiazol-2-ylmethyl)-amide.



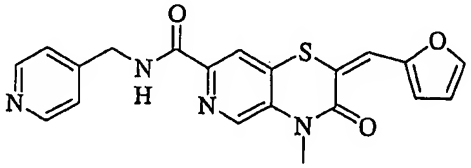
EXAMPLE 12

3-Benzylidene-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carboxylic acid benzylamide.



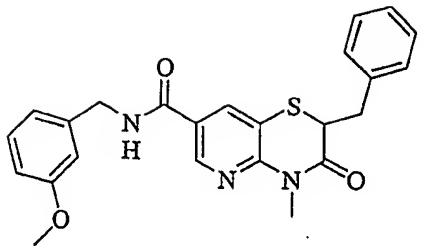
EXAMPLE 13

2-Furan-2-ylmethylene-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide.



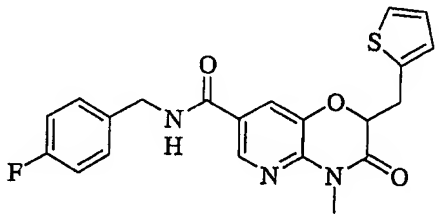
EXAMPLE 14

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-7-carboxylic acid 3-methoxy-benzylamide.



EXAMPLE 15

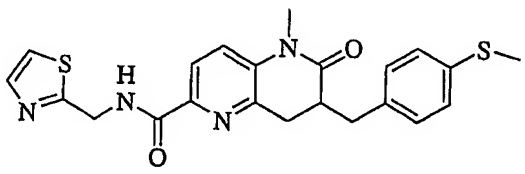
4-Methyl-3-oxo-2-thiophen-2-ylmethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carboxylic acid 4-fluoro-benzylamide.



Replacement of compound (1) in Scheme 1 with compounds (29), (34) and (37) from Schemes 4a, 4b, and 4c, and using the reaction conditions previously described in Scheme 1, the following examples can be prepared:

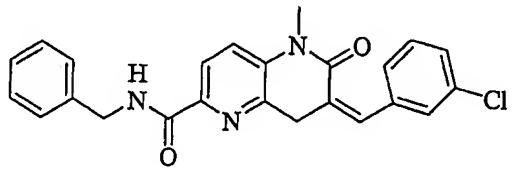
EXAMPLE 16

5-Methyl-7-(4-methylsulfanyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid (thiazol-2-ylmethyl)-amide.



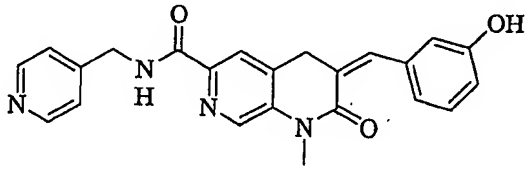
EXAMPLE 17

7-(3-Chloro-benzylidene)-5-methyl-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid benzylamide



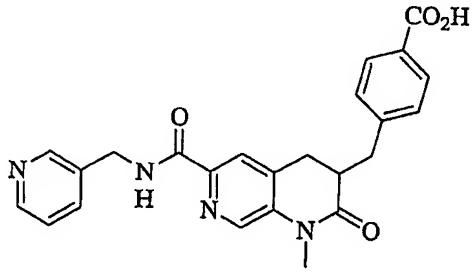
EXAMPLE 18

3-(3-Hydroxy-benzylidene)-1-methyl-2-oxo-1,2,3,4-tetrahydro-[1,7]naphthridine-6-carboxylic acid (pyridin-4-ylmethyl)-amide.



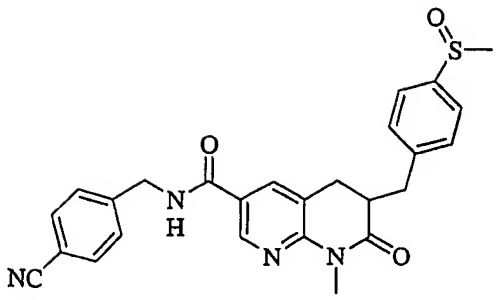
EXAMPLE 19

4-(1-Methyl-2-oxo-6-[(pyridin-3-ylmethyl)-carbamoyl]-1,2,3,4-tetrahydro-[1,7]naphthyridin-3-ylmethyl)-benzoic acid.



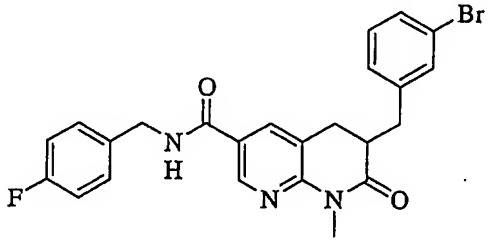
EXAMPLE 20

6-(4-Methanesufanyl-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridine-3-carboxylic acid-4-cyano-benzylamide.



EXAMPLE 21

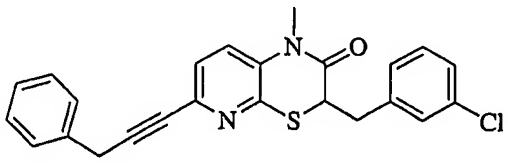
6-(3-Bromo-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-carboxylic acid 4-fluoro-benzylamide



Utilizing the reaction conditions provided in Schemes 5a and 5b, the following examples could be prepared:

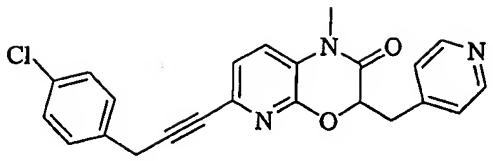
EXAMPLE 22

3-(3-Chloro-benzyl)-methyl-6-(3-phenyl-prop-1-ynyl)-1H-pyrido[2,3-b][1,4]thiazin-2-one



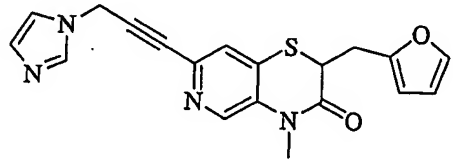
EXAMPLE 23

6-[3-(4-Chloro-phenyl)-prop-1-ynyl]-1-methyl-3-pyridin-4-ylmethyl-1H-pyrido[2,3-b][1,4]oxazin-2-one.



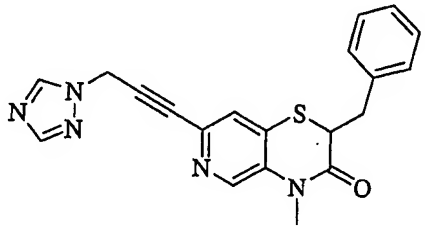
EXAMPLE 24

2-Furan-2-ylmethyl-7-(3-imidazol-1-yl-prop-1-ynyl)-4-methyl-4H-pyrido[4,3-b][1,4]thiazin-3-one



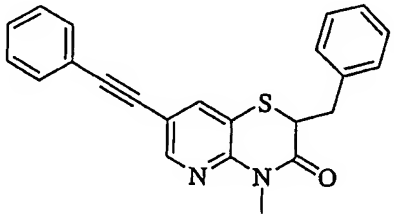
EXAMPLE 25

2-Benzyl-4-methyl-7-(3-[1,2,4]triazol-1-yl-prop-1-ynyl)-4H-pyrido[4,3-b][1,4]thiazin-3-one



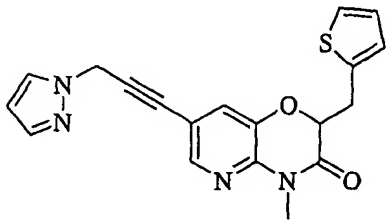
EXAMPLE 26

2-Benzyl-4-methyl-7-phenylethynyl-4-H-pyrido[3,2-b][thiazin-3-one



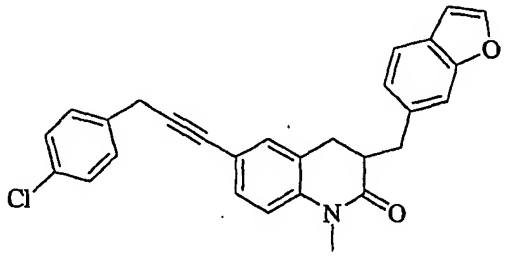
EXAMPLE 27

4-Methyl-7-(3-pyrazol-1-yl-prop-1-ynyl)-2-thiophen-2-ylmethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one



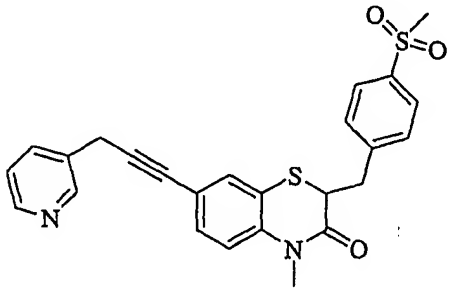
EXAMPLE 28

3-Benzofuran-6-ylmethyl-6-[3-(4-chloro-phenyl-prop-1-ynyl]-1-methyl-3,4dihydro-1H-quinolin-2-one



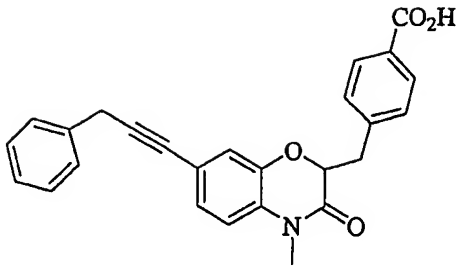
EXAMPLE 29

2-(4-Methanesulfonyl-benzyl)-4-methyl-7-(3-pyridin-3-yl-prop-1-ynyl)-4H-benzo[1,4]thiazin-3-one



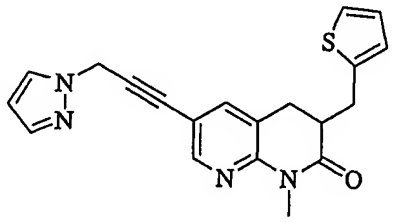
EXAMPLE 30

4-[4-Methyl-3-oxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl]-benzoic acid



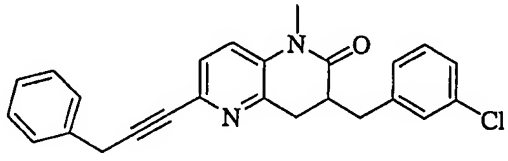
EXAMPLE 31

1-Methyl-6-(3-pyrazol-1-yl-prop-1-ynyl)-3-thiophen-2-ylmethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one



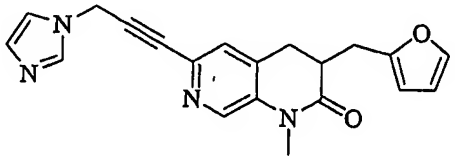
EXAMPLE 32

3-(3-Chlorobenzyl)-1-methyl-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-[1,5]naphthyridin-2-one

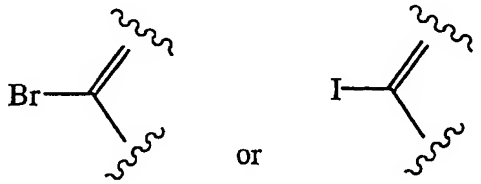


EXAMPLE 33

3-Furan-2-ylmethyl-6-(3-imidazol-1-yl-prop-1-ynyl)-1-methyl-3,4-dihydro-1H-[1,7]naphthyridin-2-one

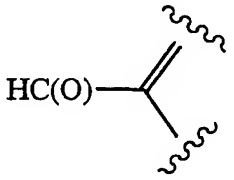


It should be appreciated that when Q is trans-(H)C=C(H), cis-(H)C=C(H), C≡C, $CH_2C{\equiv}C$, or $CF_2C{\equiv}C$ and is bonded to a sp^2 carbon atom in Formula I, a palladium catalyzed coupling of the corresponding terminal olefin or alkyne of formulas R^1-(trans-(H)C=CH_2), R^1-(cis-(H)C=CH_2), R^1-C≡CH, R^1-$CH_2C{\equiv}CH$, or R^1-$CF_2C{\equiv}CH$, wherein R^1 is as defined above, with a bromo- or iodo-substituted sp^2 carbon atom of formula:



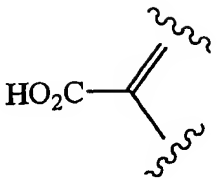
in the presence of a suitable base will yield a compound of Formula I wherein Q is trans-(H)C=C(H), cis-(H)C=C(H), C≡C, $CH_2C{\equiv}C$, or $CF_2C{\equiv}C$ and D is a group that is bonded to Q at a sp^2 carbon atom, and R^1, V, and R^2 are as defined above for Formula I. Illustrative examples of the coupling reagents and catalysts include palladium tetrakis(triphenylphosphine) or palladium(II) acetate as catalyst, a tertiary organic amine base such as triethylamine or diisopropylethylamine, a suitable solvent such as dimethylformamide ("DMF") or tetrahydrofuran ("THF"), and optionally a co-catalyst such as copper(I)iodide, at a suitable temperature such as from 0°C to 100°C, for a suitable time such as from 30 minutes to 2 days, and under an inert atmosphere such as an atmosphere of nitrogen or argon gas.

Alternatively, a corresponding aldehyde of formula



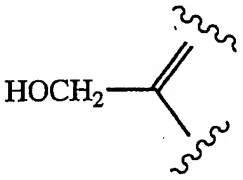
prepared as described below, may be coupled with a phosphonium ylide under Wittig olefination, or Horner-Emmons olefination, conditions to give a compound of Formula I wherein Q is trans-(H)C=C(H).

The bromo or iodo intermediates described above may be converted by conventional means to the corresponding carboxylic acid of formula



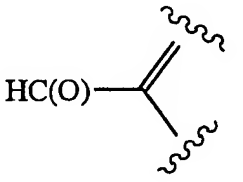
and the carboxylic acid converted by conventional means to compounds of Formula I wherein Q is OC(O), $CH(R^6)C(O)$, $OC(NR^6)$, $CH(R^6)C(NR^6)$, $N(R^6)C(O)$, $N(R^6)C(S)$, $N(R^6)C(NR^6)$, SC(O), $CH(R^6)C(S)$, or $SC(NR^6)$. Illustrative examples include coupling of the carboxylic acid with an amine to provide a compound of Formula I wherein Q is $N(R^6)C(O)$, and optionally sulfurating the resulting amide with, for example P_2S_5 to provide a compound of Formula I wherein Q is $N(R^6)C(S)$. Alternatively, the carboxylic acid may be coupled with an alcohol to provide a compound of Formula I wherein Q is OC(O).

Alternatively, the carboxylic acid may be reduced to the corresponding hydroxymethyl compound of formula



and the hydroxymethyl converted to a compound of Formula I wherein Q is OCH_2 or $N(R^6)CH_2$ by conventional means.

Alternatively, the hydroxymethyl compound may be oxidized to the corresponding aldehyde of formula

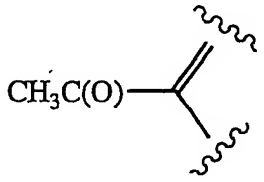


and the aldehyde coupled with hydroxylamine to give a corresponding oxime. The oxime may be chlorinated, and the chlorooxime cyclized with an olefin or alkyne to give a compound of Formula I wherein Q is a 5-membered heteroarylene.

Alternatively, the aldehyde may be prepared from the corresponding carboxylic acid by coupling the carboxylic acid with N,O-dimethylhydroxylamine

and reducing the resulting dimethylhydroxamide with a suitable hydride reducing agent such as sodium borohydride or lithium aluminum hydride.

Alternatively, the above-described carboxylic acid intermediate may be converted by conventional means to the corresponding methyl ketone of formula



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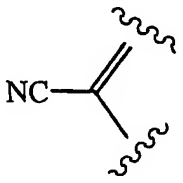
and the methyl ketone may be halogenated on methyl and coupled with various amines, alcohols, or other halogenated compounds to give a compound of Formula I wherein Q is $CH(R^6)C(O)$.

Alternatively, the above-described carboxylic acid intermediate or bromo- or iodo-intermediates may be converted by conventional means to the corresponding nitrile of formula



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and the nitrile condensed with an amine or alcohol under non-nucleophilic basic conditions (e.g., 1,8-diazaundecane) to give a compound of Formula I wherein Q is $N(R^6)C(NR^6)$ or $OC(NR^6)$, respectively.

Alternatively, compounds of Formula I wherein Q is a lactam diradical may be prepared by conventional means by cyclizing the corresponding gamma-amino acids.

The compounds of Formula I can be evaluated in standard assays for their ability to inhibit the catalytic activity of MMP enzymes. The assays used to evaluate the MMP biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions. For example, compounds of Formula I may be readily identified by assaying a test compound for inhibition of MMP-13 according to Biological Methods 1 or 2, and further assaying the test compound for allosteric

inhibition of MMP-13 according to Biological Methods 3 or 4, as described below.

The compounds of Formula I will be shown to be potent inhibitors of MMP-13 catalytic domain. Potencies, as measured by IC_{50}'s, with MMP-13 catalytic domain for the invention compounds will typically range from about 0.001 μM to about 30 μM.

Invention compounds can be further screened with full-length MMP-2, full-length MMP-7, full-length MMP-9, and MMP-14 catalytic domain to determine selectivity of the inhibitors with MMP-13 versus the other MMP enzymes also. Selectivities of the invention compounds for MMP-13 catalytic domain versus another MMP enzyme (full-length or catalytic domain), as determined by dividing the IC_{50} for the inhibitor with a comparator MMP enzyme by the IC_{50} of the inhibitor with MMP-13 catalytic domain, are expected to range from 5 to 50,000 fold.

To determine the inhibitory profiles, a compound of Formula I, or a pharmaceutically acceptable salt thereof, may be evaluated in standard assays for their ability to inhibit the catalytic activity of various MMP enzymes. The assays used to evaluate the MMP biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions. The compound of Formula I will be shown to be selective for inhibition of MMP-13CD versus MMP-1FL, MMP-2FL, MMP-3CD, MMP-7FL, MMP-9FL, MMP-12CD, and MMP-14CD with typical selectivity ranging between about 50 and about 500 fold, as measured by dividing the IC_{50} of the compound of Formula I with MMP-1FL, MMP-2FL, MMP-3CD, MMP-7FL, MMP-9FL, MMP-12CD, or MMP-14CD by the IC_{50} of the compound of Formula I with MMP-13CD.

The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate catalyzed by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye et al., in Biochemistry, 1992;31(45):11231-11235, which is incorporated herein by reference. One such assay is described below in Biological Method 1.

Some of the particular methods described below use the catalytic domain of the MMP-13 enzyme, namely matrix metalloproteinase-13 catalytic domain

("MMP-13CD"), rather than the corresponding full-length enzyme, MMP-13. It has been shown previously by Ye Qi-Zhuang, Hupe D., and Johnson L. (*Current Medicinal Chemistry*, 1996;3:407-418) that inhibitor activity against a catalytic domain of an MMP is predictive of the inhibitor activity against the respective full-length MMP enzyme.

BIOLOGICAL METHOD 1

Thiopeptolide substrates show virtually no decomposition or hydrolysis at or below neutral pH in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt. A 100 μL assay mixture will contain 50 mM of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer ("HEPES," pH 7.0), 10 mM $CaCl_2$, 100 μM thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid) (DTNB). The thiopeptolide substrate concentration may be varied, for example from 10 to 800 μM to obtain K_m and K_{cat} values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader (molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600\ M^{-1}\ cm^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

Test compounds were evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of catalytic activity of the respective enzyme.

It should be appreciated that the assay buffer used with MMP-3CD was 50 mM N-morpholinoethane sulfonate ("MES") at pH 6.0 rather than the HEPES buffer at pH 7.0 described above.

The test described above for the inhibition of MMP-13 may also be adapted and used to determine the ability of the compounds of Formula I to inhibit

the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

BIOLOGICAL METHOD 2

Some representative compounds of Formula I have been evaluated for their ability to inhibit MMP-13. Inhibitor activity versus other MMPs with the compounds may be determined using, for example, MMP-1FL, which refers to full length interstitial collagenase; MMP-2FL, which refers to full length Gelatinase A; MMP-3CD, which refers to the catalytic domain of stromelysin; MMP-7FL, which refers to full length matrilysin; MMP-9FL, which refers to full length Gelatinase B; MMP-13CD, which refers to the catalytic domain of collagenase 3; and MMP-14CD, which refers to the catalytic domain of MMP-14. Test compounds can be evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of the hydrolytic activity of the respective enzyme.

The results of the above assays with other MMPs will establish that the compounds of Formula I are potent inhibitors of MMP enzymes, and are especially useful due to their selective inhibition of MMP-13. Because of this potent and selective inhibitory activity, the compounds are especially useful to treat diseases mediated by the MMP enzymes.

Allosteric inhibitors of MMP-13 which are compounds of Formula I may be readily identified by assaying a test compound for inhibition of MMP-13 according to the methods described below in Biological Methods 3 and 4.

BIOLOGICAL METHOD 3

Fluorigenic peptide-1 substrate based assay for identifying compounds of Formula I as allosteric inhibitors of MMP-13:

Final assay conditions:

50 mM HEPES buffer (pH 7.0)

10 mM $CaCl_2$

10 μM fluorigenic peptide-1 ("FP1") substrate

0 or 15 mM acetohydroxamic acid (AcNHOH) = 1 K_d

2% DMSO (with or without inhibitor test compound)

0.5 nM MMP-13CD enzyme

Stock solutions:

1) 10X assay buffer: 500 mM HEPES buffer (pH 7.0) plus 100 mM $CaCl_2$
2) 10 mM FP1 substrate: (Mca)-Pro-Leu-Gly-Leu-(Dnp)-Dpa-Ala-Arg-NH_2 (Bachem, M-1895; "A novel coumarin-labeled peptide for sensitive continuous assays of the matrix metalloproteinases," Knight C.G., Willenbrock F., and Murphy, G., FEBS Lett., 1992;296:263-266). Is prepared 10 mM stock by dissolving 5 mg FP1 in 0.457 mL DMSO.
3) 3 M AcNHOH: Is prepared by adding 4 mL H_2O and 1 mL 10X assay buffer to 2.25 g AcNHOH (Aldrich 15,903-4). Adjusting pH to 7.0 with NaOH. Diluting volume to 10 mL with H_2O. Final solution will contain 3 M AcNHOH, 50 mM HEPES buffer (pH 7.0), and 10 mM $CaCl_2$.
4) AcNHOH dilution buffer: 50 mM HEPES buffer (pH 7.0) plus 10 mM $CaCl_2$
5) MMP-13CD enzyme: Stock concentration = 250 nM.
6) Enzyme dilution buffer: 50 mM HEPES buffer (pH 7.0), 10 mM $CaCl_2$, and 0.005% BRIJ 35 detergent (Calbiochem 203728; Protein Grade, 10%)

Procedure (for one 96-well microplate):

A. Prepared assay mixture:

1100 µL 10X assay buffer

11 µL 10 mM FP1

55 µL 3 M AcNHOH or 55 µL AcNHOH dilution buffer

8500 µL H_2O

B. Diluted MMP-13CD to 5 nM working stock:

22 µL MMP-13CD (250 nM)

1078 µL enzyme dilution buffer

C. Ran kinetic assay:

1. Dispense 2 µL inhibitor test sample (in 100% DMSO) into well.
2. Add 88 µL assay mixture and mix well, avoiding bubbles.

3. Initiate reactions with 10 μL of 5 nM MMP-13CD; mix well, avoid bubbles.
4. Immediately measure the kinetics of the reactions at room temperature.

Fluorimeter: F_{max} Fluorescence Microplate Reader & SOFTMAX PRO Version 1.1 software (Molecular Devices Corporation; Sunnyvale, CA 94089).

Protocol menu:

excitation: 320 nm	emission: 405 nm
run time: 15 min	interval: 29 sec
RFU min: -10	RFU max: 200
V_{max} points: 32/32	

D. Compared % of control activity and/or IC_{50} with inhibitor test compound ±AcNHOH.

Hydrolysis of the fluorigenic peptide-1 substrate, [(Mca)Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2; Bachem, catalog number M-1895], wherein "Mca" is (7-methoxy-coumarin-4-yl)acetyl and "Dpa" is (3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl), is used to screen for MMP-13 catalytic domain (CD) inhibitors. (Dpa may also be abbreviated as "Dnp".) Reactions (100 µL) contain 0.05 M Hepes buffer (pH 7), 0.01 M calcium chloride, 0.005% polyoxyethylene (23) lauryl ether ("Brij 35"), 0 or 15 mM acetohydroxamic acid, 10 µM FP1, and 0.1 mM to 0.5 nM inhibitor in DMSO (2% final).

After recombinant human MMP-13CD (0.5 nM final) is added to initiate the reaction, the initial velocity of FP1 hydrolysis is determined by monitoring the increase in fluorescence at 405 nm (upon excitation at 320 nm) continuously for up to 30 minutes on a microplate reader at room temperature. Alternatively, an endpoint read can also be used to determine reaction velocity provided the initial fluorescence of the solution, as recorded before addition of enzyme, is subtracted from the final fluorescence of the reaction mixture. The inhibitor is assayed at different concentration values, such as, for example, 100 µM, 10 µM, 1 µM, 100 nM, 10 nM, and 1 nM. Then the inhibitor concentration is plotted on the X-axis against the percentage of control activity observed for inhibited experiments versus uninhibited experiments (i.e., (velocity with inhibitor) divided by (velocity without inhibitor) × 100) on the Y-axis to determine IC_{50} values.

This determination is done for experiments done in the presence, and experiments done in the absence, of acetohydroxamic acid. Data are fit to the equation: percent control activity = $100/[1+(([I]/IC_{50})^{slope})]$, where [I] is the inhibitor concentration, IC_{50} is the concentration of inhibitor where the reaction rate is 50% inhibited relative to the control, and slope is the slope of the IC_{50} curve at the curve's inflection point, using nonlinear least-squares curve-fitting equation regression.

Results may be expressed as an IC_{50} Ratio (+/-) ratio, which means a ratio of the IC_{50} of the inhibitor with MMP-13 and an inhibitor to the catalytic zinc of MMP-13, divided by the IC_{50} of the inhibitor with MMP-13 without the inhibitor to the catalytic zinc of MMP-13. Compounds of Formula I which are allosteric inhibitors of MMP-13 are expected to have an IC_{50} Ratio (+/-) ratio of less than 1, and are expected to be synergistic with the inhibitor to the catalytic zinc of MMP-13 such as, for example, AcNHOH. Compounds of Formula I which are not allosteric inhibitors of MMP-13 will be inactive in the assay or will have an IC_{50} Ratio (+/-) of greater than 1, unless otherwise indicated. Results can be confirmed by kinetics experiments which are well known in the biochemical art.

BIOLOGICAL METHOD 4

Fluorigenic peptide-1 based assay for identifying allosteric inhibitors of matrix metalloproteinase-13 catalytic domain ("MMP-13CD"):

In a manner similar to Biological Method 3, an assay is run wherein 1,10-phenanthroline is substituted for acetohydroxamic acid to identify compounds of Formula I.

Animal models may be used to establish that the instant compounds of Formula I, or a pharmaceutically acceptable salt thereof, would be useful for preventing, treating, and inhibiting cartilage damage, and thus for treating osteoarthritis, for example. Examples of such animal models are described below in Biological Methods 5 and 6.

BIOLOGICAL METHOD 5

Monosodium Iodoacetate-induced Osteoarthritis in Rat Model of Cartilage Damage ("MIA Rat"):

One end result of the induction of osteoarthritis in this model, as determined by histologic analysis, is the development of an osteoarthritic condition within the affected joint, as characterized by the loss of Toluidine blue staining and formation of osteophytes. Associated with the histologic changes is a concentration-dependent degradation of joint cartilage, as evidenced by affects on hind-paw weight distribution of the limb containing the affected joint, the presence of increased amounts of proteoglycan or hydroxyproline in the joint upon biochemical analysis, or histopathological analysis of the osteoarthritic lesions.

Generally, In the MIA Rat model on Day 0, the hind-paw weight differential between the right arthritic joint and the left healthy joint of male Wistar rats (150 g) are determined with an incapacitance tester, model 2KG (Linton Instrumentation, Norfolk, United Kingdom). The incapacitance tester has a chamber on top with an outwardly sloping front wall that supports a rat's front limbs, and two weight sensing pads, one for each hind paw, that facilitates this determination. Then the rats are anesthetized with isofluorine, and the right, hind leg knee joint is injected with 1.0 mg of mono-iodoacetate ("MIA") through the infrapatellar ligament. Injection of MIA into the joint results in the inhibition of glycolysis and eventual death of surrounding chondrocytes. The rats are further administered either an invention compound or vehicle (in the instant case, water) daily for 14 days or 28 days. The invention compound is typically administered at a dose of 30 mg per kilogram of rat per day (30 mg/kg/day), but the invention compound may be administered at other doses such as, for example, 10 mg/kg/day, 60 mg/kg/day, 90-mg/kg/day, or 100 mg/kg/day according to the requirements of the compound being studied. It is well within the level of ordinary skill in the pharmaceutical arts to determine a proper dosage of an invention compound in this model. Administration of the invention compound in this model is optionally by oral administration or intravenous administration via an osmotic pump. After 7 and 14 days for a two-week study, or 7, 14, and 28 days for a four-week study, the hind-paw weight distribution is again determined. Typically, the

animals administered vehicle alone place greater weight on their unaffected left hind paw than on their right hind paw, while animals administered an invention compound show a more normal (i.e., more like a healthy animal) weight distribution between their hind paws. This change in weight distribution was proportional to the degree of joint cartilage damage. Percent inhibition of a change in hind paw joint function is calculated as the percent change in hind-paw weight distribution for treated animals versus control animals. For example, for a two week study,

Percent inhibition of a change in hind paw weight distribution

$$= \left\{ 1 - \left[\frac{(\Delta W_G)}{(\Delta W_C)} \right] \right\} \text{ X } 100$$

wherein: ΔW_C is the hind-paw weight differential between the healthy left limb and the arthritic limb of the control animal administered vehicle alone, as measured on Day 14; and

ΔW_G is the hind-paw weight differential between the healthy left limb and the arthritic limb of the animal administered an invention compound, as measured on Day 14.

In order to measure biochemical or histopathological end points in the MIA Rat model, some of the animals in the above study may be sacrificed, and the amounts of free proteoglycan in both the osteoarthritic right knee joint and the contralateral left knee joint may be determined by biochemical analysis. The amount of free proteoglycan in the contralateral left knee joint provides a baseline value for the amount of free proteoglycan in a healthy joint. The amount of proteoglycan in the osteoarthritic right knee joint in animals administered an invention compound, and the amount of proteoglycan in the osteoarthritic right knee joint in animals administered vehicle alone, are independently compared to the amount of proteoglycan in the contralateral left knee joint. The amounts of proteoglycan lost in the osteoarthritic right knee joints are expressed as percent loss of proteoglycan compared to the contralateral left knee joint control. The percent inhibition of proteoglycan loss, may be calculated as {[(proteoglycan loss

from joint (%) with vehicle) - (proteoglycan loss from joint with an invention compound)] ÷ (proteoglycan loss from joint (%) with vehicle)} × 100.

The MIA Rat data that are expected from the analysis of proteoglycan loss would establish that an invention compound is effective for inhibiting cartilage damage and inflammation and/or alleviating pain in mammalian patients, including human.

The results of these studies with oral dosing may be presented in tabular format in the columns labelled "IJFL (%+/- SEM)", wherein IJFL means Inhibition of Joint Function Limitation, "SDCES", wherein SDCES means Significant Decrease In Cartilage Erosion Severity, and "SIJWHLE", wherein SIJWHLE means Significant Increase in Joints Without Hind Limb Erosion.

The proportion of subjects without hind limb erosions may be analyzed via an *Exact Sequential Cochran-Armitage Trend* test (*SAS*® Institute, 1999). The Cochran-Armitage Trend test is employed when one wishes to determine whether the proportion of positive or "Yes" responders increases or decreases with increasing levels of treatment. For the particular study, it is expected that the number of animals without joint erosions increased with increasing dose.

The ridit analysis may be used to determine differences in overall erosion severity. This parameter takes into account both the erosion grade (0 = no erosion, I = erosion extending into the superficial or middle layers, or II = deep layer erosion), and area (small, medium and large, quantified by dividing the area of the largest erosion in each score into thirds) simultaneously. The analysis recognizes that each unit of severity is different, but does not assume a mathematical relationship between units.

Another animal model for measuring effects of an invention compound on cartilage damage and inflammation and/or pain is described below in Biological Method 6.

BIOLOGICAL METHOD 6

Induction of Experimental Osteoarthritis in Rabbit ("EOA in Rabbit"):

Normal rabbits are anaesthetized and anteromedial incisions of the right knees performed. The anterior cruciate ligaments are visualized and sectioned.

The wounds are closed and the animals are housed in individual cages, exercised, and fed ad libitum. Rabbits are given either vehicle (water) or an invention compound dosed three times per day with 30-mg/kg/dose or 10-mg/kg/dose. The invention compound may be administered at other doses such as, for example, 3 times 20 mg/kg/day or 3 times 60 mg/kg/day according to the requirements of the invention compound being studied. The rabbits are euthanized 8 weeks after surgery and the proximal end of the tibia and the distal end of the femur are removed from each animal.

Macroscopic Grading

The cartilage changes on the femoral condyles and tibial plateaus are graded separately under a dissecting microscope (Stereozoom, Bausch & Lomb, Rochester, NY). The depth of erosion is graded on a scale of 0 to 4 as follows: grade 0 = normal surface; Grade 1 = minimal fibrillation or a slight yellowish discoloration of the surface; Grade 2 = erosion extending into superficial or middle layers only; Grade 3 = erosion extending into deep layers; Grade 4 = erosion extending to subchondral bone. The surface area changes are measured and expressed in mm^2. Representative specimens may also be used for histologic grading (see below).

Histologic Grading

Histologic evaluation is performed on sagittal sections of cartilage from the lesional areas of the femoral condyle and tibial plateau. Serial sections (5 um) are prepared and stained with safranin-O. The severity of OA lesions is graded on a scale of 0 - 14 by two independent observers using the histologic-histochemical scale of Mankin *et al.* This scale evaluates the severity of OA lesions based on the loss of safranin-O staining (scale 0 - 4), cellular changes (scale 0 - 3), invasion of tidemark by blood vessels (scale 0 - 1) and structural changes (scale 0 - 6). On this latter scale, 0 indicates normal cartilage structure and 6 indicates erosion of the cartilage down to the subchondral bone. The scoring system is based on the most severe histologic changes in the multiple sections.

Representative specimens of synovial membrane from the medial and lateral knee compartments are dissected from underlying tissues. The specimens

are fixed, embedded, and sectioned (5 um) as above, and stained with hematoxylin-eosin. For each compartment, two synovial membrane specimens are examined for scoring purposes and the highest score from each compartment is retained. The average score is calculated and considered as a unit for the whole knee. The severity of synovitis is graded on a scale of 0 to 10 by two independent observers, adding the scores of 3 histologic criteria: synovial lining cell hyperplasia (scale 0 - 2); villous hyperplasia (scale 0 - 3); and degree of cellular infiltration by mononuclear and polymorphonuclear cells (scale 0 - 5): 0 indicates normal structure.

Statistical Analysis

Mean values and SEM is calculated and statistical analysis was done using the Mann-Whitney U-test.

The results of these studies would be expected to show that an invention compound would reduce the size of the lesion on the tibial plateaus, and perhaps the damage in the tibia or on the femoral condyles. In conclusion, these results would show that an invention compound would have significant inhibition effects on the damage to cartilage.

The foregoing studies would establish that an invention compound is effective for the inhibition of cartilage damage and inflammation and/or alleviating pain, and thus useful for the treatment of osteoarthritis or rheumatoid arthritis in human, and other mammalian disorders. Such a treatment offers a distinct advantage over existing treatments that only modify pain or inflammation or and other secondary symptoms. The effectiveness of an invention compound in this model would indicate that the invention compound will have clinically useful effects in preventing and/or treating cartilage damage, pain and/or inflammation.

Administration according to the invention method of an invention compound to a mammal to treat the diseases listed above is preferably, although not necessarily, accomplished by administering the compound, or a salt thereof, in a pharmaceutical dosage form.

The compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be prepared and administered according to the invention method in a wide variety of oral and parenteral pharmaceutical dosage forms. Thus, the

compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered by inhalation, for example, intranasally. Additionally, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component an invention compound. The invention compounds generally are present in a concentration of about 5% to about 95% by weight of the formulation.

For preparing pharmaceutical compositions from the compounds of Formula I, or a pharmaceutically acceptable salt thereof, (i.e., the active component) pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations are preferred. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. Powders suitable for intravenous administration or administration by injection may be lyophilized.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from about 5% to about 70%, total, of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and

lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing an appropriate quantity of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.01 to 1000 mg, preferably 1 to 500 mg according to the

particular application and the potency of the active components. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents to treat the above-listed diseases, the compounds of Formula I, or a pharmaceutically acceptable salt thereof, are administered at a dose that is effective for treating at least one symptom of the disease or disorder being treated. The initial dosage of about 1 mg/kg to about 100 mg/kg daily of the active component will be effective. A daily dose range of about 25 mg/kg to about 75 mg/kg of the active component is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the particular invention compound being employed in the invention combination. Determination of the proper dosage for a particular situation is within the skill of the art as described above. Typical dosages will be from about 0.1 mg/kg to about 500 mg/kg, and ideally about 25 mg/kg to about 250 mg/kg, such that it will be an amount that is effective to treat the particular disease or disorder being treated.

A preferred composition for dogs comprises an ingestible liquid peroral dosage form selected from the group consisting of a solution, suspension, emulsion, inverse emulsion, elixir, extract, tincture and concentrate, optionally to be added to the drinking water of the dog being treated. Any of these liquid dosage forms, when formulated in accordance with methods well known in the art, can either be administered directly to the dog being treated, or may be added to the drinking water of the dog being treated. The concentrate liquid form, on the other hand, is formulated to be added first to a given amount of water, from which an aliquot amount may be withdrawn for administration directly to the dog or addition to the drinking water of the dog.

A preferred composition provides delayed-, sustained- and/or controlled-release of an invention compound. Such preferred compositions include all such dosage forms which produce ≥ 40% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 3 fold the active component's ED_{40} for at least 2 hours; preferably for at least 4 hours; preferably for at least 8 hours; more preferably for at least 12 hours; more preferably still for at least 16 hours; even more preferably still for at least 20 hours; and most

preferably for at least 24 hours. Preferably, there is included within the above-described dosage forms those which produce ≥ 40% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours, preferably for at least 2 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours. More preferably, there is included the above-described dosage forms which produce ≥ 50% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours, preferably for at least 4 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours.

The following Formulation Examples 1 to 8 illustrate the invention pharmaceutical compositions. When the formulations comprise the invention compound and a pharmaceutically acceptable carrier, diluent, or excipient, they contain a cartilage damage treating effective amount or a therapeutically effective amount such as, for example, an anti-osteoarthritic effective amount of the invention compound. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 1

Tablet Formulation:

Ingredient	Amount (mg)
An invention compound	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The invention compound, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders.

The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for inhibiting cartilage damage or treating osteoarthritis.

FORMULATION EXAMPLE 2

Coated Tablets:

The tablets of Formulation Example 1 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 3

Injection vials:

The pH of a solution of 500 g of an invention compound and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the invention compound.

FORMULATION EXAMPLE 4

Suppositories:

A mixture of 25 g of an invention compound, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 25 mg of the invention compound.

FORMULATION EXAMPLE 5

Solution:

A solution is prepared from 1 g of an invention compound, 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the invention compound.

FORMULATION EXAMPLE 6

Ointment:

500 mg of an invention compound is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the invention compound.

FORMULATION EXAMPLE 7

Capsules:

2 kg of an invention compound are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the invention compound.

FORMULATION EXAMPLE 8

Ampoules:

A solution of 2.5 kg of an invention compound is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the invention compound.

The following Formulation Examples 9 to 16 illustrate the invention pharmaceutical compositions containing an invention combination in a single formulation with a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 9

Tablet Formulation:

Ingredient	Amount (mg)
An invention compound	25
A COX-2 inhibitor	20
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	120

The invention compound or COX-2 inhibitor, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 10

Coated Tablets:

The tablets of Formulation Example 9 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 11

Injection vials:

The pH of a solution of 250 g of a COX-2 inhibitor, 500 g of an invention compound, and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 12.5 mg of COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 12

Suppositories:

A mixture of 50 g of a COX-2 inhibitor, 25 g of an invention compound, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 50 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 13

Solution:

A solution is prepared from 0.5 g of a COX-2 inhibitor, 1 g of an invention compound, 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 12.5 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 14

Ointment:

100 mg of a COX-2 inhibitor, 500 mg of an invention compound is mixed with 99.4 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 5 mg of the COX-2 inhibitor and 25 mg of the invention compound.

FORMULATION EXAMPLE 15

Capsules:

2 kg of a COX-2 inhibitor and 20 kg of an invention compound are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the COX-2 inhibitor and 250 mg of the invention compound.

FORMULATION EXAMPLE 16

Ampoules:

A solution of 2.5 kg of a COX-2 inhibitor and 2.5 kg of an invention compound is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg each of the COX-2 inhibitor and the invention compound.

While it may be desirable to formulate a COX-2 inhibitor and an invention compound together in one capsule, tablet, ampoule, solution, and the like, for simultaneous administration, it is not necessary for the purposes of practicing the invention methods. A COX-2 inhibitor and an invention compound alternatively can each be formulated independently in any form such as, for example, those of any one Formulation Examples 1 to 16, and administered to a patient either simultaneously or at different times.

The following examples illustrate the invention pharmaceutical compositions containing discrete formulations of the active components of an invention combination and a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 17

Tablet Formulation of an invention compound:

Ingredient	Amount (mg)
An invention compound	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

An invention compound, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated

with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet.

Injection vial formulation of a COX-2 inhibitor:

The pH of a solution of 500 g of a COX-2 inhibitor and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the COX-2 inhibitor.

Such tablets containing the invention compound can be administered to a human from one to four times a day for treatment of the above-listed diseases, and the injection solutions containing the COX-2 inhibitor can be administered to a human 1 or 2 times per day, wherein the administration by injection is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 18

Coated Tablets containing an invention compound:

The tablets of Formulation Example 17 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

Capsules containing valdecoxib or celecoxib:

2 kg of a COX-2 inhibitor are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the COX-2 inhibitor.

Such coated tablets containing the invention compound can be administered to a human from one to four times a day for treatment of the above-listed diseases, and the capsules containing the COX-2 inhibitor can be administered to a human 1 or 2 times per day, wherein the administration of the capsules is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

Still further, it should be appreciated that the invention methods comprising administering an invention combination to a mammal to treat diseases

or disorders listed above may be used to treat different diseases simultaneously. For example, administration of a COX-2 inhibitor in accordance with the invention combination may be carried out as described above to treat inflammation, arthritic pain, pain associated with menstrual cramping, and migraines, while an invention compound may be administered to treat OA or inhibit cartilage damage.

As shown above, the invention methods comprising administering an invention compound offer a distinct advantage over existing treatments for diseases such as OA that comprise cartilage damage, wherein the existing treatments modify pain or secondary symptoms, but do not show a disease modifying effect.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

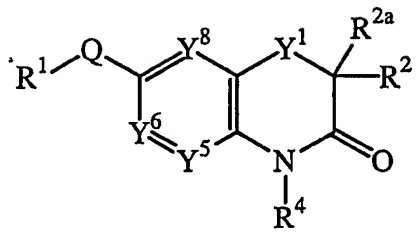
All references cited above are hereby incorporated by reference herein.

Having described the invention method, various embodiments of the invention are hereupon claimed.

CLAIMS

What is claimed is:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

R^{2a} is H or C_1-C_6 alkyl; or

R^2 and R^{2a} are taken together with the carbon atom to which they are both bonded to form a group $C{=}C(H)R^2$, wherein R^2 is as defined above;

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$;

H_2N;

$(C_1\text{-}C_6$ alkyl)-N(H);

$(C_1\text{-}C_6$ alkyl)$_2$-N;

$(C_1\text{-}C_6$ alkyl)-C(O)O-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl);

$(C_1\text{-}C_6$ alkyl)-N(H)$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)$_2$-$NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-$S(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl)$_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-$S(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

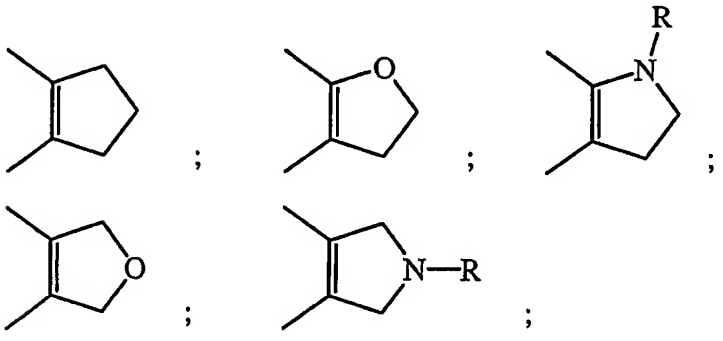
wherein each substituent on a carbon atom may further be independently selected from:

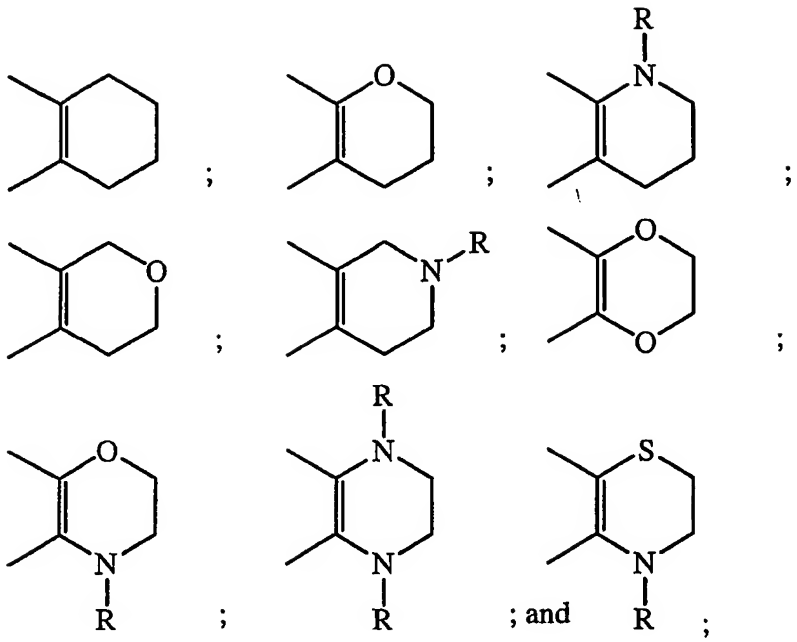
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

m is an integer of 0 or 1;

Y^1 is O, S, S(O), $S(O)_2$, or CH_2;

Y^5, Y^6, and Y^8 are each independently $C(R^5)$ or N;

R^4 and each R^5 are each independently selected from the groups:

H;

CH_3;

CH_3O;

$CH=CH_2$;

HO;

CF_3;

CN;

HC(O);

$CH_3C(O)$;

HC(NOH);

H_2N;

(CH_3)-N(H);

$(CH_3)_2$-N;

$H_2NC(O)$;

(CH_3)-N(H)C(O); and

(CH3)2-NC(O);

Q is selected from:

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(S)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

SC(O);

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

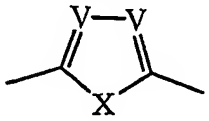
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CH_2$;

$CF_2C{\equiv}C$; and

$C{\equiv}CF_2$;



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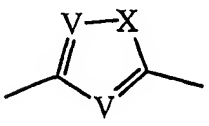

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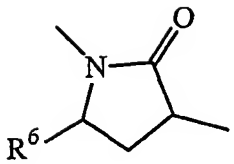

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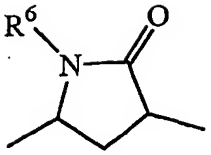

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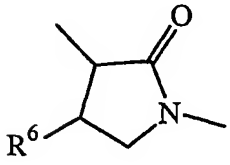

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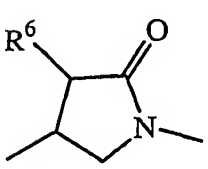

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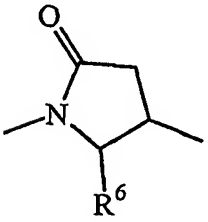

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Each R^6 independently is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V is independently C(H) or N;

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 $S(O)_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O

and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any $(C_1\text{-}C_6$ alkyl$)_2$-N group, the $C_1\text{-}C_6$ alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and

wherein each group and each substituent recited above is independently selected.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y^5, Y^6, and Y^8 are each $C(R^5)$ or one of Y^5, Y^6, and Y^8 is N and the other two of Y^5, Y^6, and Y^8 is $C(R^5)$, wherein each R^5 is independently defined as above, Y^1 is O or $S(O)_2$, and Q is $N(R^6)C(O)$ or C≡C.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y^5, Y^6, and Y^8 are each $C(R^5)$ or one of Y^5, Y^6, and Y^8 is N and the other two of Y^5, Y^6, and Y^8 is $C(R^5)$, wherein each R^5 is independently defined as above, Y^1 is CH_2, and Q is $N(R^6)C(O)$ or C≡C.

4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is independently selected from:

Phenyl-$(C_1\text{-}C_8$ alkylenyl);

Substituted phenyl-$(C_1\text{-}C_8$ alkylenyl);

5- or 6-membered heteroaryl-$(C_1\text{-}C_8$ alkylenyl);

Substituted 5- or 6-membered heteroaryl-$(C_1\text{-}C_8$ alkylenyl);

8- to 10-membered heterobiaryl-$(C_1\text{-}C_8$ alkylenyl); and

Substituted 8- to 10-membered heterobiaryl-$(C_1\text{-}C_8$ alkylenyl); and

R^2 is independently selected from:

Phenyl-$(C_1\text{-}C_8$ alkylenyl$)_m$;

Substituted phenyl-$(C_1\text{-}C_8$ alkylenyl$)_m$;

5- or 6-membered heteroaryl-$(C_1\text{-}C_8$ alkylenyl$)_m$;

Substituted 5- or 6-membered heteroaryl-$(C_1\text{-}C_8$ alkylenyl$)_m$;

8- to 10-membered heterobiaryl-$(C_1\text{-}C_8$ alkylenyl$)_m$; and

Substituted 8- to 10-membered heterobiaryl-$(C_1\text{-}C_8$ alkylenyl$)_m$;

wherein m is an integer of 0 or 1; and

wherein each group and each substituent is independently selected.

5. The compound according to Claim 1, selected from:

3-Benzylidene-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 4-methylsulfanyl-benzylamide;

3-(3,5-Difluoro-4-hydroxy-benzyl)-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (pyrimidin-5-ylmethyl)-amide;

3-Biphenyl-4-ylmethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid 3-fluoro-benzyl amide;

5-Methyl-7-(4-methylsulfanyl-benzyl)-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid (thiazol-2-ylmethyl)-amide;

7-(3-Chloro-benzylidene)-5-methyl-6-oxo-5,6,7,8-tetrahydro-[1,5]naphthyridine-2-carboxylic acid benzylamide;

3-(3-Hydroxy-benzylidene)-1-methyl-2-oxo-1,2,3,4-tetrahydro-[1,7]naphthridine-6-carboxylic acid (pyridin-4-ylmethyl)-amide;

4-(1-Methyl-2-oxo-6-[(pyridin-3-ylmethyl)-carbamoyl]-1,2,3,4-tetrahydro-[1,7]naphthyridin-3-ylmethyl)-benzoic acid;

6-(4-Methanesufanyl-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridine-3-carboxylic acid-4-cyano-benzylamide;

6-(3-Bromo-benzyl)-8-methyl-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-carboxylic acid 4-fluoro-benzylamide;

4-Methyl-3-oxo-2-(4-trifluoromethyl-benzylidene)-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid 3-methoxy-benzylamide;

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid benzylamide;

2-(3-Chloro-4-fluoro-benzyl)-4-methyl-3-oxo3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxylic acid (quinolin-3-ylmethyl)-amide;

3-Benzylidene-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-6-carboxylic acid benzylamide;

4-Methyl-3-oxo-2-thiophen-2-ylmethyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carboxylic acid 4-fluoro-benzylamide;

4-Methyl-2-(4-methyl-benzylidene)-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-cyano-benzylamide;

2-(4-Chloro-benzyl)-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazone-7-carboxylic acid-benzylamide;

4-Methyl-3-oxo-2-pyridin-3-ylmethyl-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide;

2-Furan-2-ylmethyl-4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-carboxylic acid 4-methoxy-benzylamide;

3-(3-Chloro-benzyl)-1-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazine-6-carboxylic acid (thiazol-2-ylmethyl)-amide;

2-Furan-2-ylmethylene-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[4,3-b][1,4]thiazine-7-carboxylic acid (pyridin-4-ylmethyl)-amide; and

2-Benzyl-4-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-7-carboxylic acid 3-methoxy-benzylamide;

or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1, selected from:

3-Benzofuran-6-ylmethyl-6-[3-(4-chloro-phenyl-prop-1-ynyl]-1-methyl-3,4dihydro-1H-quinolin-2-one;

1-Methyl-6-(3-pyrazol-1-yl-prop-1-ynyl)-3-thiophen-2-ylmethyl-3,4-dihydro-1H-[1,8]naphthyridin-2-one;

3-(3-Chlorobenzyl)-1-methyl-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-[1,5]naphthyridin-2-one;

3-Furan-2-ylmethyl-6-(3-imidazol-1-yl-prop-1-ynyl)-1-methyl-3,4-dihydro-1H-[1,7]naphthyridin-2-one;

6-[3-(4-Chloro-phenyl)-prop-1-ynyl]-1-methyl-3-pyridin-4-ylmethyl-1H-pyrido[2,3-b][1,4]oxazin-2-one;

4-Methyl-7-(3-pyrazol-1-yl-prop-1-ynyl)-2-thiophen-2-ylmethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one;

4-[4-Methyl-3-oxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl]-benzoic acid;

3-(3-Chloro-benzyl)-methyl-6-(3-phenyl-prop-1-ynyl)-1H-pyrido[2,3-b][1,4]thiazin-2-one;

2-Furan-2-ylmethyl-7-(3-imidazol-1-yl-prop-1-ynyl)-4-methyl-4H-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-7-(3-[1,2,4]triazol-1-yl-prop-1-ynyl)-4H-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-7-phenylethynyl-4H-pyrido[3,2-b][thiazin-3-one;

2-(4-Methanesulfonyl-benzyl)-4-methyl-7-(3-pyridin-3-yl-prop-1-ynyl)-4H-benzo[1,4]thiazin-3-one;

3-(3-Chloro-benzyl)-1-methyl-4,4-dioxo-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-4λ^6-pyrido[2,3-b][1,4]thiazin-2-one;

2-Furan-2-ylmethyl-7-(3-imidazol-1-yl-prop-1-ynyl)-4-methyl-1,1-dioxo-1,4-dihydro-2H-1λ^6-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-1,1-dioxo-7-(3-[1,2,4]triazol-1-yl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-pyrido[4,3-b][1,4]thiazin-3-one;

2-Benzyl-4-methyl-1,1-dioxo-7-phenylethynyl-1,4-dihydro-2H-1λ^6-pyrido[3,2-b][thiazin-3-one; and

2-(4-Methanesulfonyl-benzyl)-4-methyl-1,1-dioxo-7-(3-pyridin-3-yl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-benzo[1,4]thiazin-3-one;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

8. A method for treating arthritis, comprising administering to a patient suffering from an arthritis disease a nontoxic antiarthritic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

9. A method for treating osteoarthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

10. A method for treating rheumatoid arthritis, comprising administering to a patient suffering from rheumatoid arthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/03537

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5415 C07D265/36 C07D279/16 C07D417/14 C07D413/12
C07D417/06 C07D215/22 C07D401/12 C07D498/04 C07D513/04
C07D471/04 C07D405/06 A61P29/00 A61K31/4375 A61K31/4704

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02497 A (NOVARTIS ERFIND VERWALT GMBH ;HECKENDORN ROLAND (CH); AUBERSON YVE) 21 January 1999 (1999-01-21)	1,3
A	page 42, line 1; claims 6,9,11,12	2,4-10
X	US 4 792 561 A (BRUNO JOHN J ET AL) 20 December 1988 (1988-12-20)	1,3
A	column 2, line 5-45 column 11, line 1 -column 12, line 25; claims 1,7,8,14; examples 9,12	2,4-10
X	US 4 886 809 A (TAMADA SHIGEHARU ET AL) 12 December 1989 (1989-12-12)	1,3
A	column 23 column 90, line 15 -column 92, line 23; examples 54,58,71,81,108,109	2,4-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2003	20/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gavriliu, D

INTERNATIONAL SEARCH REPORT

PCT/IB 03/03537

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4709 A61K31/538 A61K31/5383 A61K31/542

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 4 454 130 A (NAKAGAWA KAZUYUKI ET AL) 12 June 1984 (1984-06-12) column 35, line 1 -column 38, line 20; examples 1,2	1,3 2,4-10
X A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN Database accession no. 1977:106613 XP002262267 compound with RN:62001-02-9 abstract & PATENT ABSTRACTS OF JAPAN & JP 51 098294 A (OTSUKA PHARMACEUTICAL CO., LTD., JAPAN), 30 August 1976 (1976-08-30) abstract	1,3 2,4-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gavriliu, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 14, 31 December 1998 (1998-12-31) & JP 10 259176 A (JAPAN TOBACCO INC), 29 September 1998 (1998-09-29) abstract; examples 143-205,212	1-10
Y	WO 2000 063197 A (SUMITOMO PHARMACEUTICALS CO., LTD., JAPAN;HADIDA RUAH, SARA SABINA) 26 October 2000 (2000-10-26) page 200, line 5 -page 206; examples 365,433,439,848,908,909,912-914,919-926; tables 5,28	1-10
Y	WO 98 43959 A (BIRD THOMAS GEOFFREY COLERICK ;ZENECA PHARMA SA (FR); ZENECA LTD () 8 October 1998 (1998-10-08) page 20, line 10-22; examples 17,19 page 2, line 7-12	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present Claim 1 relates to an extremely large number of possible compounds. In fact, Claim 1 contains so many options, variables, possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT arises to such an extent as to render a meaningful search of the Claim 1 impossible. The Claim 1 can in no way be considered to be a reasonable generalisation of the actual examples since it include numerous possibilities which cannot be considered as equivalents, homologues or analogues of the examples. Consequently, the search was carried out for those parts of the application which do appear to be clear (concise and supported by the examples), namely for the compounds for which Y1=CO, S or CH2 and Q is either a N(R6)C(O) moiety or a triple bond as defined in Claims 2 and 3. All the examples have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/03537

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

PCT/IB 03/03537

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		US 6251913 B1	26-06-2001
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Drawings are not displayable due to the volume of the data (more than 200 drawings).

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1]
the hydroxamic acid derivative shown by the formula [1], its prodrug, or those salts that are permitted pharmacologically -- here, X C1-C2 alkylene (the alkyl by which this alkylene may be permuted --) The cycloalkyl which may be permuted, the hetero cycloalkyl which may be permuted, Permute by the aryl which may be permuted, or the heteroaryl which may be permuted. It is o-arylene which may be permuted, or o-hetero arylene which may be permuted, Y1 is -O-, -S-, -S(O)-, or -S(O)2-, and Y2 is O or S.
One side of R1 and R3 is -(CHR4) n-(CR five R6)-CO-NHOH. Another side of R1 and R3 They are hydrogen, the alkyl which may be permuted, or cycloalkyl which may be permuted. R2 Hydrogen, the alkyl which may be permuted, the alkenyl which may be permuted, It is the alkynyl which may be permuted, the cycloalkyl which may be permuted, or hetero cycloalkyl which may be permuted, or is C1-C10 alkylidene by which R2 and R3 may be permuted by becoming together.
Respectively R4, R5, and R6 independently Hydrogen, the alkyl which may be permuted, The alkenyl which may be permuted, the alkynyl which may be permuted, The alkylthio which may be permuted and of which the alkoxy ** permutation may be done, Are the cycloalkyl which may be permuted, the hetero cycloalkyl which may be permuted, the aryl which may be permuted, or heteroaryl which may be permuted, or R5 combines with R4 or R6. The cycloalkane or the hetero cycloalkane which may be permuted which may be permuted with the carbon atom which they combine may be formed.
n is the integer of 0 to 4. However, when C1-C10 alkylidene by which R2 and R3 may be permuted by becoming together is expressed, X is not methylene permuted by phenyl or pyridyl (this phenyl and pyridyl may be permuted by methyl or methoxy).
[Claim 2]
C1-C by which X was permuted by -Z-Ar -- the hydroxamic acid derivative of claim 1 which is the aryl with which it is o-arylene or o-hetero arylene which may be permuted which may be permuted, Z is single bond or alkylene, and Ar may be permuted 2 alkylene, or heteroaryl which may be permuted, its prodrug, or those salts that are permitted pharmacologically.
[Claim 3]
They are the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1 whose A1 are the aryl with which X is one of the radicals shown by the formula, and Ar1 may be permuted, or heteroaryl which may be permuted, and is o-phenylene or mono-cyclo o-hetero arylene and R8 and whose R9 are hydrogen or a substituent independently respectively.
[Claim 4]
One of the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1-3 whose Y1 is -S-, -S(O)-, or -S(O)2-.
[Claim 5]
One of the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1-4 whose n is 0, 1, or 2.

[Claim 6]
One of the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1-5 whose n is 0.
[Claim 7]
the hydroxamic acid derivative of claim 1 shown by the formula [2], its prodrug, or those salts that are permitted pharmacologically -- here The phenyl by which Y2, R4, R5, and R6 are defined by claim 1, and Ar2 may be permuted, It is the naphthyl which may be permuted, the monochrome which may be permuted, or bicyclo heteroaryl, and Y3 is -S-, -S(O)-, or -S(O)2-. Respectively R10 and R11 independently It is hydrogen or the alkyl which may be permuted and n1 is the integer of 0, 1, or 2.
[Claim 8]
The hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 7 whose n1 is 0.
[Claim 9]
the hydroxamic acid derivative of claim 1 shown by the formula [3], its prodrug, or those salts that are permitted pharmacologically -- here Y2, R4, R5, and R6 are defined by claim 1, and A1, R8, and R9 are what is defined by claim 3. Respectively R12 and R13 independently It is hydrogen or the alkyl which may be permuted, Y3 is -S-, -S(O)-, or -S(O)2-, and n2 is the integer of 0, 1, or 2.
[Claim 10]
the hydroxamic acid derivative of claim 1 shown by the formula [3'], its prodrug, or those salts that are permitted pharmacologically -- Y2, R4, R5, and R6 are defined by claim 1, A1 is defined by claim 3 here, Y3, n2, R12, and R13 are defined by claim 9, R14 is hydrogen or a substituent, and R15 is a substituent.
[Claim 11]
The hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 9-10 whose n2 is 0 and R12 and whose R13 are hydrogen or the permuted alkyl group independently respectively.
[Claim 12]
One of the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1-11 whose Y2 is -O-.
[Claim 13]
The remedy constituent containing the support or the diluent permitted by one hydroxamic acid derivative of claims 1-12, its prodrug or those salts that are permitted pharmacologically, and the pharmaceutical-sciences target.
[Claim 14]
The inhibition approach of the matrix metal protease characterized by processing matrix metal protease with one of the hydroxamic acid derivative, its prodrug, or those salts that are permitted pharmacologically of claim 1-12.
[Claim 15]

(19)日本国特許庁（ＪＰ）　(12)公表特許公報（Ａ）　(11)特許出願公表番号
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（Ｐ2002－542238Ａ）
(43)公表日　平成14年12月10日（2002.12.10）

(51)Int.Cl.[7]	識別記号	ＦＩ	ﾃｰﾏｺｰﾄﾞ(参考)
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Ａ６１Ｋ 31/426		Ａ６１Ｋ 31/426	４Ｃ０３６
31/427		31/427	４Ｃ０５６
31/4439		31/4439	４Ｃ０６３
31/445		31/445	４Ｃ０７１

審査請求　未請求　予備審査請求　有　（全202頁）　最終頁に続く

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(86)(22)出願日　平成12年４月19日（2000.4.19）
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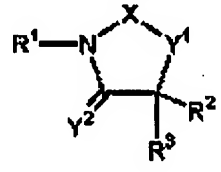
(33)優先権主張国　米国（ＵＳ）

(71)出願人　住友製薬株式会社
大阪府大阪市中央区道修町２丁目２番８号
(72)発明者　スカーラト　ジェラード　ロバート
アメリカ合衆国　カリフォルニア州　92037　ラ　ホヤ、バージニア　ウェイ　1121
(72)発明者　ハディダ　ルアー　サラ　サビーネ
アメリカ合衆国　カリフォルニア州　92122　サン　ディエゴ、ノベル　ドライブ　＃1411　3717
(72)発明者　西村　民樹
大阪府豊中市曽根東町２－11－７－201
(74)代理人　弁理士　久保山　隆　（外３名）

最終頁に続く

(54)【発明の名称】　ヒドロキサム酸誘導体

(57)【要約】
マトリックス金属プロテアーゼを阻害する式［１］で示されるヒドロキサム酸誘導体、そのプロドラッグ又はそれらの薬学的に許容される塩。



［１］

(TRANSLATION)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
533791		
International application No.	International Filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP2005/003821	28. 02. 2005	02. 03. 2004

Applicant:

SUMITOMO PHARMACEUTICALS CO., LTD.

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of:
      ☐ the international application in the language in which it was filed
      ☒ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.
2. ☐ Certain claims were found unsearchable (see Box No. II).
3. ☒ Unity of invention is lacking (see Box No. III).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. 1
      ☐ as suggested by the applicant
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be puglished with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/003821

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [ ] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [X] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purposes of search

2. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/003821

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

The compounds of claims 11-18 considerably differ in the basic skeleton of the compounds themselves from the compounds and uses thereof of claims 1-10. In view of this, there is no matter common between claims 11-18 and claims 1-10 which is regarded as a special technical feature. No technical relationship can be found in the meaning of Rule 13 of the Regulations under the PCT.

Therefore, the subject matters of claims 1-10 and those of claims 11-18 do not comply with the requirement of unity of invention.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/003821

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D279/16, A61K31/5415, A61P29/00, 43/00, C07C59/64, 69/734, 205/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D279/16, A61K31/5415, A61P29/00, 43/00, C07C59/64, 69/734, 205/56

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2005
Kokai Jitsuyo Shinan Koho 1971-2005 Toroku Jitsuyo Shinan Koho 1994-2005

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y ✓	JP 2002-128769 A (Sumitomo Pharmaceuticals Co., Ltd.), 09 May, 2002 (09.05.02), Claims; Par. No. [0020] (Family: none)	1-10
Y	JP 2002-542238 A (Sumitomo Pharmaceuticals Co., Ltd.), 10 December, 2002 (10.12.02), Claims; pages 128 to 138; Par. No. [0117] & WO 2000/063197 A1	1-10
A	WO 2003/055851 A1 (Sumitomo Pharmaceuticals Co., Ltd.) 10 July, 2003 (10.07.03), (Family: none)	1-10

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 June, 2005 (03.06.05)	21 June, 2005 (21.06.05)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/003821

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/014389 A1 (WARNER-LAMBERT CO., LLC.), 19 February, 2004 (19.02.04), (Family: none)	1-10